The Journal of Pediatrics

VOL. 45 OCTOBER, 1954 No. 4

Editor's Note: The important subject of the resuscitation of the newborn infant is decidedly controversial. Part of this involves the Bloxsom Air Lock which has been installed in a number of newborn nurseries in the last few years. While some physicians are enthusiastic as to its practical value, others have attacked the physiological concepts upon which it is based, and have questioned the interpretation of the statistics which have been published in support of its value.

Recently Dr. Bloxsom submitted the following paper for publication, stressing the value of the Air Lock, but not discussing the objections and criticisms in regard to it which have been raised. In other words, it presents but one side of a controversial subject. The Editorial Board, after reviewing the paper, made a proposal to Dr. Bloxsom, which he accepted, that it would publish the paper provided it was followed by a discussion of the underlying concepts of pulmonary ventilation in the newborn infant and other points in the paper. The editor suggested five of the names of those taking part in the discussion, and five were suggested by Dr. Bloxsom. The group includes physiologists, pathologists, obstetricians, and pediatricians.

The JOURNAL takes no side in the controversy, or in favor of or against the Air Lock. The Editorial Board felt that this use of Dr. Bloxsom's paper would make an interesting and much-needed discussion of an important controversial subject. The JOURNAL particularly wishes to thank those who have participated in the discussion. It is left to the individual reader to form his own opinion.

NEWER THERAPEUTIC PROCEDURES DESIGNED TO PREVENT ABNORMAL PULMONARY VENTILATION IN THE NEWBORN INFANT

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POTTER[1] has classified 44 per cent of neonatal deaths as owing to abnormal pulmonary ventilation. This group of newborn infants offers the greatest opportunity to further lower the neonatal infant mortality in every community. The success or failure of handling the problem of lowering neonatal infant mortality through adequate pulmonary ventilation depends upon the obstetrician, the anesthetist, and the pediatrician functioning as a team.

Obstetrical practices conducive to low infant mortality are well known. The part of certain analgesics and anesthetics in decreasing or increasing neonatal infant mortality is recognized. In addition to the general measures available to the obstetrician and the anesthetist for producing a

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Presented to the Continental Gynecological Travel Club March 12, 1954, Methodist Hospital, Houston, Texas.

low neonatal infant mortality, recent investigative work has spotlighted certain newer special measures that should be undertaken as treatment upon the newborn infant in difficulty by the obstetrician or anesthetist immediately upon delivery, and continued by the pediatrician when he is contacted, in an effort to continue this downward trend. The theory and the practical measures for the application of this newer knowledge for the further lowering of neonatal infant mortality rates will be discussed in detail in this paper.

Practical steps taken to correct and prevent further abnormal pulmonary ventilation will reduce neonatal infant mortality. Bloxsom and Angelique[2] have demonstrated that neonatal term infant mortality in a hospital will be surprisingly lowered when the Bloxsom Air Lock is widely used in that hospital. The first Air Lock was introduced in the St. Joseph's Maternity Hospital in Houston on Jan. 2, 1950. In 1949, the year previous to the introduction of the Air Lock, there were 5,918 term infants delivered in this hospital with thirty-seven deaths, a rate of sixty-three deaths per 10,000 term infant deliveries. In 1952, the third year after the introduction of the Air Lock and in which period five Air Locks were widely used in this hospital, there were 5,702 term deliveries with twenty-one deaths, giving a death rate of thirty-seven per 10,000 term deliveries, a 41 per cent drop. This rate still remains, however, about four times that of a good obstetrical maternal rate of one maternal death per 1,000 live deliveries, a hoped-for but never obtainable goal in neonatal infant mortality.

Not only term infant mortality, but premature infant mortality can be lowered when the Air Lock is used to full advantage. In 1949 there were 377 premature infant births with eighty-four deaths in this hospital, giving a premature death rate of 22.28 per cent, or 2,228 premature infant deaths per 10,000 premature infant deliveries. This rate is in the low range of currently quoted good premature neonatal mortality. In 1952, the third year after the introduction of the Air Lock, there were 452 premature deliveries with sixty-eight deaths, giving a premature death rate of 15.04 per cent or 1,504 premature infant deaths per 10,000 premature infant deliveries. This is a drop of 32.5 per cent in the premature infant neonatal death rate of this hospital to a new low of 15.04 per cent and is one of the best quoted in the literature.[3]

The above term and premature neonatal infant mortality rate decreases show a beginning has been made in the forward progress of neonatal infant salvage. The challenge remains now of a further lowering of the neonatal infant death rate in this hospital.

After the use of the Air Lock was started, it soon became apparent that a number of evolutionary physiological steps, not one, were essential for the survival of the infant at birth. The Air Lock seemed capable of initiating and taking several necessary early measures for the infant's survival. Important following steps have been found now to be later vital for the infant's survival. All the steps for the newborn infant's "successful operation oxygenation" are listed be-

low in order of what seems to be their importance.

1. As Eastman[4] has pointed out, the number one step necessary for the newborn infant to take at birth is to get oxygen into his blood stream so that his respiratory center can function. Probably it is equally important to remove any excess carbon dioxide from the infant's blood so that his respiratory center will be sensitive to the available oxygen tension in his blood.

2. The next necessary step for the infant is the establishing of a workable physiological barrier over which oxygen and carbon dioxide can pass in the infant's lungs. Faure-Fremiet[6] showed that before birth the connective tissue of the parenchyma of the lung continues to increase while the epithelium apparently does not increase sufficiently to cover the alveolar walls. Stewart[7] stated that through the degeneration of the connective tissue, space is provided for expansion of the alveoli. The cuboidal epithelial cell cytoplasm is rendered plastic through the imbibition of fluid. Accordingly, it is less firm and is more capable of deformation. A change takes place whereby the cuboidal cell is changed to a flat form, either by pressure brought about by gasping movements

TABLE I. OXYGEN SATURATION READINGS OBTAINED BY AN INFANT OXIMETER ON INITIATION OF RESPIRATIONS BY AN APNEIC INFANT BEING OXYGENATED IN THE AIR LOCK

Mother—eclamptic	Total sedation over 36 hours		
Morphine sulfate	2 grains		
Meperidine hydrochloride	200 mg.		
Paraldehyde	30 c.c.		
Phenobarbital sodium	25 grains		
Minutes after delivery	Oximeter readings in % oxygen saturation		
3 (adjustment oximeter)	15		
5 (in Air Lock with cycling)	50		
6 (infant made initial gasp)	50		
7	65		
9 (irregular respirations started)			
	Pressures in Air Lock		
	3.5 lb.	3 lb.	1 lb.
9	77	83	
10	75	86	
14	83	94	96
16	86	95	95
20	87	97	104

This initial step is made relatively easy by keeping the infant in a high concentration of oxygen and subjecting him to barospiration through all available pathways for supplemental oxygenation. This can be carried out in the Air Lock, which is the only instrument that provides accessory barospiration for the newborn infant. The ordinary means of resuscitation, as pointed out by Best and Taylor,[5] are bound in advance to fail because of the partial inadequate expansion or nonexpansion of the fetal lung. The oxygenation chart (Table I) shows the increase in blood oxygen saturation when a handicapped anoxic newborn infant was treated in the Air Lock for anoxia. Oxygenation by barospiration was successfully carried to a level at which the infant could take over and survive the immediate postdelivery stage by having a sufficient oxygen tension in his blood.

in utero described by Ahlfeld[8] or by the first postnatal inspirations. During the process of expansion, either the various epithelial cells must be sufficiently plastic to line the alveoli completely or else for a time some portion of the alveolar wall must be free of epithelium. It is believed by Bloxsom[9] that some premature infants and the cesarean section infant in difficulty attempt during that period to plug and protect those areas by hyaline membrane formation in an effort to prevent pulmonary capillary leakage. Only when the hyaline membrane becomes pathologically widespread is it a danger to life. The hyaline membrane is seen almost exclusively in the cesarean section infant and the premature infant, the two types of infants whose cuboidal pulmonary epithelial cells do not have a chance of adequate metamorphosis. The cesarean section infant's cuboidal cells are mature enough to metamorphosize, but they do not have the stimuli of pressures to initiate that metamorphosis. The premature infant's cuboidal cells through labor have the stimuli of pressures but are not mature enough to undergo metamorphosis.

Farber and Wilson[10] stated that it is normal for a variable amount of atelectasis to persist for several days. The lungs of the normal term infant customarily expand gradually over a period of a few days. No effort was made clinically to take advantage of this gradual metamorphosis of the low cuboidal cell of the lung until the Air Lock was devised. The metamorphosis starting before labor, continuing during labor, and ending after delivery of the infant with the full expansion of his lungs several days later is the result of the stimuli of pressures during labor or respiratory movement pressures after delivery. These metamorphic changes clinically seem to be hastened by the pressures generated either during labor or postdelivery by the Air Lock, thus permitting the infant to more quickly stabilize himself at a viable respiratory level for the cross-cellular transfer of oxygen and carbon dioxide.

3. At this time it is believed by Bloxsom[11] that the intracellular binding cement (hyaluronic acid) also may hinder progressive expansion of the pulmonary alveoli and the separation of the squamous alveolar cells of some infants to provide functioning alveolar sacs. Wilson and Farber[12] stated that relatively great force is required to overcome the cohesion of the moist surfaces of the collapsed airless lung. They believe that the first breath of the newborn infant may be its most difficult one, and that for a variable period after birth especially vigorous inspirations must be maintained. Gruenwald[13] has shown that surface tension counteracts the entrance of air in the fetal lung, and the fetal lung areas separate more easily when a surface-acting substance as amyl acetate is added to the separating solution. Gruenwald recommended that the addition of some surface-acting substance to the air or oxygen which was being spontaneously breathed by the infant be introduced to relieve the initial atelectasis.

The nebulization of hyaluronidase (Alidase) as reported by Bloxsom[11] in Alevaire to offset the binding action of the hyaluronic acid between the low cuboidal cells before they become flattened epithelial cells of the

alveoli lining the fetal alveolar sacs clinically seems to aid in permitting the rapid expansion of the alveolar sacs through the neutralization of the intracellular binding cement, hyaluronic acid.

Intracellular cement liquefying substance (hyaluronidase) may be carried down into all available pulmonary spaces by means of a therapeutic mist of 1 to 3 μ radius-sized particles of Alevaire. The correct-sized mist of Alevaire acting as a vehicle of the hyaluronidase is produced either by a DeVilbiss No. 40 nebulizer or by the Ne-Bu-Jet, which is a continuous-acting nebulizer built around the DeVilbiss No. 40 jet and turbulent chamber and attachable to the Gordon Armstrong incubator. It is interesting to note in passing that the umbilical cord of the newborn infant is very rich in hyaluronic acid.[14]

4. In addition, the tenacious mucus in the lungs per se may hinder proper expansion. It is essential, therefore, that a mucous-liquefying action be provided to the therapeutic-sized mist entering into the infant's open pulmonary spaces. Miller and Boyer[15] have shown that Alevaire, a mixture of a new nontoxic detergent Triton A-20 in a concentration of 0.125 per cent, in combination with sodium bicarbonate 2 per cent and glycerin 5 per cent, provides a satisfactory mucous-liquefying agent. The mist must be in the 1 to 3 μ radius-sized particles for full therapeutic application in the terminal alveolar sacs. Abramson[16] stated that "aerosol delivery should be certified by the manufacturer of the nebulizers and that claims should be supported by acceptable laboratory evidence." The DeVilbiss No. 40 nebulizer has been found by Abramson to deliver sufficient mist in the therapeutic-sized range of 1 to 3 μ in radius to warrant its use with both epinephrine and penicillin. The use of nonstandardized nebulizers may not lead to the full therapeutic possibilities of correct-sized mist. Therefore, the physician, when he orders mist therapy, should specify a standardized generator as the DeVilbiss No. 40 or a generator built around the DeVilbiss No. 40 nebulizer in order to take full advantage of maximal aerosol delivery in the therapeutic zone of the lungs.

5. With the lungs being progressively expanded and aerated, the probability of a pneumonitis is present. It has been shown by post-mortem examination of the lungs of a series of infants dying within the first twenty-four hours of life that a pneumonitis is present in approximately 38 per cent of those infants. In order to prevent this infection, penicillin for heavy topical application in high concentration must be nebulized into the lungs through the therapeutic-sized mist of Alevaire and hyaluronidase as well as being given intramuscularly.

CASE REPORT

Baby K. K., St. Joseph's Maternity Hospital No. 876, was born to a white female, aged 38 years, para i, gravida ii. Labor started at 7 P.M. on Feb. 8, 1954, after thirty weeks of gestation. Delivery was at 9:01 P.M. of a 4 pound 3¾ ounce male infant after a median episiotomy. The infant cried spontaneously, and the color was good after delivery. At 9:40 P.M. the infant was sent to the Premature Nursery, with grunting respirations and marked sternal retractions. He was given 300,000 units of penicillin; he was placed in the Air Lock, and cycling started. At

10:55 P.M. nebulization of Alevaire carrying hyaluronidase and penicillin was started by means of a Ne-Bu-Jet. The mixture for nebulization contained 500 c.c. of Alevaire, 500 units of Alidase (hyaluronidase), and 500,000 units of penicillin (soluble).

At 4 A.M. on February 9, some five hours after starting the nebulization and cycling in the Air Lock, the infant's color was good, the grunting had ceased, and the respirations became a great deal improved. Steady pressure was then used in the Air Lock of 2 pounds. At 6 A.M. on February 9 the respirations again became slightly irregular, and grunting was noticed occasionally. Cycling of the Air Lock was started again. At 4 P.M. on February 9, seventeen hours after cycling and nebulization had been started, the infant's color was good, the respirations were quite regular, and retractions had ceased. Periodic cycling was discontinued.

The infant's birth weight on February 8 was 4 pounds 3¾ ounces. On February 10 the weight was 4 pounds 1½ ounces, and on February 11 the weight was 3 pounds 15 ounces. Nothing had been given by mouth. These weights are given to show the usual extremely small amount of weight loss when an infant has available for absorption through his lungs a large amount of therapeutic-sized mist of water. Actually what occurs is that the lungs in this type of treatment expand in a colloidal water-oxygen-air therapeutic-sized mist system with the water in the continuous phase and containing an intracellular cement-liquefying substance with penicillin, instead of attempting expansion in a colloidal air-water system (100 per cent humidity) with no surface tension-acting agent. The continuation of the colloidal water oxygen-air therapeutic-sized mist system must be carried out for a number of days to prevent a possible alveolar collapse leading to a reabsorption atelectasis. At the present time accessory fluid intake of the infant in therapeutic-sized mist appears to be of little importance.[9, 17]

The infant had no further complications; on February 22 the weight was 4 pounds 12 ounces, and he was discharged to his mother for breast feeding.

SUMMARY

No one form of therapy or the use of any one instrument upon the newborn infant can provide theoretically optimal physiological results. Ideal treatment to prevent abnormal pulmonary ventilation in the newborn infant must be centered around the following five principles:

1. Barospiration in the Air Lock serves as the initial introduction of oxygen to increase time to enable the respiratory center to function and to remove carbon dioxide. Accessory oxygenation theoretically can be provided only by barospiration because of the nonexpansion of the lungs.

2. Pressure changes must be exerted upon the infant in the Air Lock similar to those produced at labor to aid in the metamorphosis of the low cuboidal cell lining the alveolar sacs for the more efficient transfers of oxygen and carbon dioxide.

3. The lungs are expanded in a colloidal water-oxygen-air therapeutic-sized mist system with the water in the continuous phase and continuing an intracellular cement-liquefying substance (hyaluronidase) instead of attempting expansion in a colloidal air-water system (100 per cent humidity) with no surface-acting agent. The continuation of the colloidal water-oxygen-air therapeutic-sized mist system must be for a sufficiently long period to prevent a possible reabsorption atelectasis.

4. The tenacious mucus is liquefied by a detergent.

5. Pulmonary infection is prevented by antibiotics intramuscularly and in concentrated local alveolar sac application with penicillin through proper aerosol therapy.

The treatment of the newborn infant with these five principles results in an all-out clinical program for aiding during the immediate postdelivery period in the progressive physiological alteration of the fetal lung to assume an efficient extrauterine functioning.

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Discussion by Dr. James L. Wilson, Ann Arbor:

These comments on the paper by Bloxsom are being written at the invitation of the editor of THE JOURNAL OF PEDIATRICS, and with the foreknowledge of Dr. Bloxsom. I find this task very difficult to execute since, quite candidly, the paper seems to me to be so full of mixtures of facts and speculation, with references to sound research work followed by implications that such work supports Bloxsom's ideas, without any substantial sequence, that any thorough criticism of the paper would seem to me to be necessarily as long as the original paper itself. Therefore, I can only comment on a few of the many points which I think are particularly misleading. The present paper of Dr. Bloxsom apparently does not pretend to present new data but offers a general program for the reduction of neonatal mortality based on the acceptance of two or three therapeutic plans which are either not generally accepted and of questionable soundness, or still very much in the experimental stage.

The therapeutic value of the Bloxsom Air Lock is obviously the most pertinent one to this discussion since reference to it occurs throughout the paper, although no description of the apparatus is given in this paper. The present publication cannot be understood without review of the original papers of Bloxsom, describing and advocating the use of this device.

The Bloxsom Air Lock is a machine in which an infant is completely enclosed, where he can be subjected to rather slow changes of air pressure over considerable ranges, the changes in pressure being produced by either oxygen or air in chosen concentration. The idea of producing an alveolar gas exchange by intermittent changes in pressure, without the necessity of volume changes in the lung, is not a new one and rests upon sound physical principles which were well established many years ago by Thünberg* who devised an apparatus, which he called a "barospirator," to produce artificial respiration. It seems likely, from lack of any reference to Thünberg, that Dr. Bloxsom was not aware of Thünberg's work when he began writing about his machine, although use of the word "barospirator" in the present paper, which is the term that Thünberg invented for his device, suggests that he now is aware of it. However, the Bloxsom Air Lock differs from the Thünberg "barospirator" in essential features in that the pressure changes are not rapid enough or great enough to produce anything like effective alveolar ventilation, although it is conceivable that some small gas exchange might be brought about. This has been well worked out in years past by Thünberg and in recent years by Dr. Barach who will, I hope, comment on it more directly. All I can say at the present time is that the Bloxsom Air Lock, on the basis of a great deal of work by others† (and I have seen no experimental data by Bloxsom to indicate the opposite opinion), cannot accomplish any adequate, or probably important, alveolar air exchange.

The actual claims of Dr. Bloxsom for his Air Lock were based upon less sound physical principles than the Thünberg effect. One was that oxygen under pressure could be absorbed through the skin. Much work in the past supplies not a bit of evidence for this, and no supporting evidence has ever been given by Bloxsom that there is any significant absorption of oxygen through the skin under any oxygen pressure which has ever been used. An implication that he still believes that oxygen can be absorbed through the skin, however, is in the phrase that he uses in this paper, that "all available pathways" to get oxygen to the lungs are to be used in his therapeutic programs. I know of no pathway that admits oxygen to the blood or tissues except the one through the bronchial airways.

A major claim for the Air Lock is that it will force out bronchial tree secretions during the phase of diminishing pressure in the Air Lock or, in other words, produce a cough effect. This principle also has been subjected to a great deal of investigation by Dr. Alvan Barach and will receive no further comment from me except the statement that I do not believe the rate of change of pressure is nearly adequate to bring about any substantial effect toward expelling bronchial secretions.

Statistical data about reduction in mortality are offered, which means nothing to me since they are uncontrolled data and all sorts of other variations may have occurred in the clinics in which the data were collected during the time of the introduction of this Air Lock and other procedures. In other words, no controlled observations that I know of have been offered where only the Air Lock has been the variant allowed.

I can pick out a few instances to illustrate the point that fact and imagination or speculation are so thoroughly mixed in the Bloxsom paper that it takes a person with considerable patience and experience in the fields of respiratory physiology to untangle them, although in casual perusal of the paper, the arguments may seem persuasive. In regard to getting oxygen into the blood stream, it is stated that "this initial step is made relatively easy by keeping the infant in a high concentration of oxygen and sub-

*Thünberg, T.: Abderhalden's Handbuch der biologischen Arbeitsmethoden, Abt. 5, Teil 1, 561, 1827, and Drinker, C. K.: New Apparatus for Artificial Respiration: The Barospirator of Professor T. Thünberg. J. Indus. Hyg. 10: pp. 7-12, 1928.

†Apgar, V., and Kreiselman, J.: Am. J. Obst. & Gynec. 65: 45-52, 1953.

jecting him to barospiration through all available pathways for supplemental oxygenation. This can be carried out in the Air Lock, which is the only instrument that provides accessory barospiration for the newborn infant." This last statement is, of course, in part true since no similar apparatus is commercially available which attempts to imitate the pressure respiration changes devised by Thünberg, as has been commented on before. It does not follow, however, that the Air Lock possesses efficient action in any way.

Bloxsom goes on to state that, "The ordinary means of resuscitation as pointed out by Best and Taylor are bound in advance to fail because of partial inadequate expansion or non-expansion of fetal lungs." This, in my opinion, is thoroughly wrong. I do not find where Best and Taylor made any such statement, but if they did, I believe it is incorrect, if by ordinary means of respiration we refer to those customarily used in hospitals, such as intermittent positive pressure over the mouth, or the use of the Drinker type respirator. They are not bound to fail because of partial inadequate expansion of fetal lung, although it is clear that no method of artificial respiration in the newborn has been shown to be consistently satisfactory. If there were not "partial inadequate expansion of fetal lung" there would be little reason for any attempt at resuscitation.

Dr. Bloxsom furnishes us briefly with one example of measured oxygenation levels in an infant, treated by the Air Lock. This baby was born with the handicap that his mother was given 2 grains of morphine and 25 grains of sodium phenobarbital in the day and a half before delivery, and we should expect the trouble that occurred. The data are derived from the use of the oximeter, but no description of the detailed use of the device is furnished. It was noted that the first reading of the baby, born with respiratory failure, was 15, three minutes after delivery, and that this is an "adjustment oximeter" reading. The Air Lock was used, and three minutes later the reading was 50 per cent. Subsequently it goes up a bit more as a few respirations took place. We have, therefore, one period of three minutes before any observed respirations occurred, when the oximeter reading changed from 15 to 50 per cent. This might have indicated a beneficial effect of the Air Lock, but is all quite unconvincing to me with the inadequate description and data furnished. We can only speculate on what data might be found in any baby born under the circumstances that this one was, that was not given any oxygen or given oxygen in the ordinary way. Babies have survived similar ill-advised maternal narcosis without any medical assistance, of course.

A long discussion is given us about the "metaplasia" of the epithelium lining the air passage of the lung. It is stated that, "Cuboidal epithelium cell cytoplasm is rendered plastic through the inhibition of fluid. Accordingly, it is less firm and more capable of deformation." The implication seems to be that the Bloxsom Air Lock does something about bringing about this "inhibition of fluid" which makes cells "plastic." This is clearly in the field of purest speculation. A great deal of thought by many students has been given to this apparent change in respiratory passage epithelium and I know of no certain solution that has been reached. We certainly are not convinced that the word "metamorphosis" is the correct one or that the change of the lining cells is not a pure physical one due to distention of the lung probably after birth, but possibly in part before birth; I know of no data or even good theory that would suggest that the change is brought about by compression of the child's total body by changes in atmospheric pressure or by uterine contractions. Nevertheless, the implication throughout this paper is that the Bloxsom Air Lock does do something in a mysterious and remarkable way through some histological

change to make the expansion of the lung later more easy.

Reference is made to Farber and Wilson who state that a variable amount of atelectasis persists for several days. This is now, of course, well established, but Bloxsom goes on with an unclear transition from this reference to imply that the Air Lock takes advantage somehow of this delayed expansion to bring about advantageous "metamorphosis." No evidence whatever is presented.

Considerable emphasis has been given to the use of hyaluronidase nebulized by oxygen to aid the absorption of the so-called hyaline membranes. The whole problem of "hyaline membranes" is thoroughly confused. Many people, including myself, do not believe there is good evidence that the so-called hyaline membrane is a clinical entity or anything but an accidental pathological finding without specific etiological significance, which is almost inevitable where death occurs with agonal dyspnea and fluid in the air passages. The use of Alevaire has recently been subjected to a rather neat study by Silberman and Anderson, reported before the Society for Pediatrics Research in May of this year. This is the only study that I know of where the procedure has been subjected to any critical evaluation with any attempt at experimental work or at controlled observations. Silberman and Anderson concluded that no evidence was obtained to prove this procedure valuable. This, of course, has nothing to do with the use of the Bloxsom Air Lock, but is presented by Bloxsom as part of a general program of established ways of reducing neonatal mortality. It is, I believe, another example of the vague generalized statements about effective therapy that encumber this article without being justified by critical study or presentation of physiological data.

I believe this article with its optimistic program will be very misleading to many practitioners who are eagerly looking for practical help in one of the most difficult fields of medicine.

Discussion by Dr. James L. Whittenberger, Boston:

I am glad to accept the invitation to discuss Dr. Bloxsom's essay. Since his description of the Air Lock in 1950 I have awaited the presentation of evidence for the specific advantages claimed for this device; I regret to say that no such information has yet been presented. Until such evidence is obtained, I consider it misleading to call the Air Lock a mechanism of resuscitation and to magnify the differences between the Air Lock and any other type of O_2 incubator.

To resuscitate is to revive, to restore from apparent death. It is generally accepted that the cardinal requirement of resuscitation is effective artificial respiration. Effective artificial respiration is the provision of alveolar ventilation at a rate sufficient to meet the metabolic needs, in a manner which does not harm the baby. Metabolic needs in this instance are the provision of sufficient O_2 to the tissues and the elimination of a corresponding amount of CO_2. For this exchange, an integrated complex of activities is necessary; at a minimum these include the presence of an adequately large alveolar surface, with constant refreshment of alveolar gases by pulmonary ventilation and constant replacement of the corresponding pulmonary capillary blood by pulmonary blood flow.

The need for alveolar ventilation can be minimized for O_2 by enrichment of the inspired air to high levels of O_2 concentration. With 60 or 70 per cent O_2 in the inspired air, the one or two breaths per minute provided by the Air Lock could be sufficient for basal metabolic needs. However, it has been shown abundantly in experimental animals and man that no such compromise can be made in regard to CO_2 elimination. If pulmonary ventilation is not maintained at levels proportional to CO_2 production, respiratory acidosis must occur; if alveolar ventilation consisted of one or two ordinary breaths per minute, severe progressive acidosis would occur, regardless of the level of oxygenation.

The level of alveolar ventilation provided by normal respiratory mechanisms in a resting newborn baby is obtained from an average tidal volume of 17 ml. which is repeated thirty to forty times per minute. Any form of artificial respiration should provide at least this much pulmonary ventilation.

Relatively little is known about the forces required to distend the lungs of a newborn baby and about the volume of air in the lungs at progressive increments of time after birth. It is known that newborn babies are normally capable of creating a lung-distending pressure of at least 40 cm. H_2O.* It is also known that newborn lambs develop pressures in this range to inflate their lungs. In a similar way, various types of pressure breathing machines or mouth-to-mouth insufflation have been used to distend the lungs. After the initial inflation, rhythmic changes of pressure bring about the tidal ventilation.

A different principle of artificial respiration is the use of density changes to move molecules into and out of the lungs, as a substitute for changes of lung volume. A normal alveolar ventilation rate could be achieved if the density changes were of sufficient magnitude, or if the density change were adjusted to give a normal tidal volume and the cycle were repeated at a normal respiratory frequency. In practice, the Air Lock produces a density change sufficient to give a nearly normal tidal volume, but the cycle is repeated only once or twice per minute, rather than a normal thirty to forty times per minute. It is not fair to consider the Air Lock a barospirator until such time as its cycling frequency is increased to the vicinity of thirty per minute. Even if this were done, the apparatus would not work unless the lungs contained an adequate amount of air space. The Air Lock itself has *no* tendency to distend the lungs, since the changes of pressure are applied virtually simultaneously to the internal pulmonary surfaces and the outside surface of the body. The device would therefore be completely ineffective unless the infant's own muscular efforts had opened up the lungs.

Dr. Bloxsom is technically correct in saying that the Air Lock, as used, causes increased O_2 absorption through the skin; this is equally true of any incubator in which the O_2 is raised to the same partial pressure. No quantitative studies have been made of respiratory gas exchange through the skin of newborn babies. The studies done on adult human beings and several species of animals indicate that, in air, skin exchange of O_2 and CO_2 is at approximately 1 per cent of the pulmonary rate. If the diffusion gradient were increased by O_2 enrichment of the atmosphere, possibly three or four times as much O_2 could be absorbed; even this could hardly be considered an important avenue of absorption, inasmuch as the absorbed O_2 is used almost entirely or exclusively in the skin itself. Again the figure is not known for babies, but in adult human beings the skin constitutes approximately 15 per cent of the body weight. The skin therefore could account for the increased O_2 uptake, without implicating benefit to the brain or other vital tissues.

Bloxsom concludes his paper with what he calls five "principles" of ideal treatment to prevent abnormal pulmonary ventilation in the newborn infant. What is meant by abnormal ventilation is not defined. If insufficient quantity of ventilation per unit time is the intended meaning, the Air Lock does not come close to satisfying the ventilatory needs of an apneic infant. If the intended meaning of abnormal is that the distribution of ventilation is unfavorable, there is no evidence presented on this point, and there is no reason to expect that the Air Lock should have a favorable influence. There is likewise no evidence that the Air Lock can relieve or prevent atelectasis, that it provides breathing exercise, that it combats acute pulmonary edema, or that it provides favorable conditions for the diffusion of O_2. These earlier claims, as well as the present ones made for the

*Smith, C. A.: J. PEDIAT. 20: 338, 1942.

use of detergent aerosols, are quite unsubstantiated; they appear to be based upon speculations made by Bloxsom out of his clinical experience.

In conclusion, irrespective of the possible merits of the Air Lock, Bloxsom's present paper does not answer any of the questions he has previously evoked; his unsupported hypotheses do not add to the sum of valid pediatric knowledge. The Air Lock in its present form does not deserve to be called a resuscitator. It is quite possibly a good incubator, though an unnecessarily complex one.

Discussion by Dr. Alvan L. Barach, New York City:

A sound physiologic basis for the contentions of Dr. Bloxsom, in the use of the Bloxsom Air Lock, does not, in fact, exist. First of all, the ventilation required for the apneic infant would be about twenty to thirty times that accomplished in the Air Lock by an alteration of 1 to 3 pounds pressure at a cycling rate of 1.2 cycles per minute. As shown by the studies of Thünberg, as well as those made in our clinic over a period of many years, ventilation of the lungs by alteration in air density requires the use of a cycling rate of twenty-five times a minute with pressures of this order. Our studies on anesthetized dogs as well as on clinical subjects have demonstrated that carbon dioxide accumulation frequently does occur even with this degree of ventilation unless there is added to the alternating pressure a method by which the tracheobronchial resistance is compensated for. There would be no need to compensate for tracheobronchial resistance in the Bloxsom Air Lock since the pressure change is induced so gradually. By the same token, there is not actual locally applied pressure on the lungs. There is simply a change in air density, equivalent to altering the position of the body in space (i.e., altitude), in this case approximately 4,000 feet from sea level.

The air flow rate during inspiration and expiration that is accomplished by changes in air density in the Bloxsom apparatus is less than that achieved by infants and children during normal respiration, and obviously could have no effect on the movement of secretions outward from the alveoli to the mouth. As shown in our recent study of mechanically induced cough, expiratory flow rates of 6,000 to 10,000 c.c. per second are required for effective elimination of retained mucus. It is a misconception to assume that the alternating pressures simulate uterine contractions since there is no actual alternating pressure applied, except as indicated above, to the body as a whole; in other words, comparable to that of altering the position of the body in space by changing the altitude.

The studies of Apgar and Kreiselman indicated clearly enough that in dogs made apneic by drug depression the Bloxsom Air Lock was unsuccessful in oxygenating the animals or in removing carbon dioxide. The conclusion of these authors coincides with that of my own that any clinical advantage found in its use would be related to the provision of an increased oxygen tension in the air breathed by the infant, a therapeutic aim that could be accomplished manifestly much more simply. Furthermore, ventilation by volume resuscitation or a change in the volume of the lungs produced by intermittent inspiratory pressure breathing would be more likely to have value in respect to initiation and maintenance of respiratory function than the so-called barospiration provided in the Bloxsom Air Lock. The Air Lock does not initiate measures for the infant's survival beyond that of providing oxygen and an extremely slight mechanism for the removal of carbon dioxide, namely, 3 to 5 per cent of the ventilation required.

In respect to aerosol therapy, the studies of Talbot, Quimby, and Barach, LeMere, and others, on absorption of radioactive aerosols, and the measures by which optimal antibiotic aerosols were studied through blood and sputum levels, are reviewed in my book and, in summary, indicate that a particle size of one micron in

radius is likely to reach the alveoli and be absorbed and that a particle size mist of 2.5 to 5.0 micra in diameter is more likely to lodge on the bronchial mucous membrane. The DeVilbiss No. 40 and the Vaponefrin nebulizers and others that provide this range of particle size are likely to be satisfactory for the administration of antibiotic and bronchodilator aerosols. Conclusions based on the administration of solid particles do not apply. Antibiotic aerosols are of value in those clinical entities in which a high sputum concentration of the drug is desired, either because the organism is resistant to the concentration obtained by intramuscular injection of the drug or because of impaired diffusion of the antibiotic to the bronchial mucous membrane. Whether or not penicillin or other antibiotic aerosols are indicated in infants has not, to my knowledge, been determined. In addition, the evidence for the use of aerosols consisting of Alevaire and hyaluronidase is conflicting and dubious, at best, as indicated by studies of Silverman from the Babies Hospital, Columbia University. Finally, reference to the studies of Day and those of Apgar would be appropriate in a paper of this kind.

When I first read Dr. Bloxsom's article, I wondered why he did not increase the cycling rate to an extent that would be physiologically comprehensible in terms of at least one of the objectives which he had in mind.

Discussion by Dr. Clement A. Smith, Boston:

Of the many points in Dr. Bloxsom's paper which provoke discussion, my comments will be limited to relatively few.

Under heading 1, Dr. Bloxsom states that "The ordinary means of resuscitation . . . are bound in advance to fail because of the partial inadequate expansion or nonexpansion of the fetal lung." This sweeping statement is misleading, unless it means that a degree of nonexpansion is sometimes reached at which various resuscitative measures are useless. Actually this must seldom occur, for many simple procedures appear to help in bringing about breathing in the majority of infants to whom they are applied.

Dr. Bloxsom is thus on dubious ground in putting forward the principle of "barospiration" as "the only method" likely to succeed in infants with unexpanded lungs. This principle, introduced by Thünberg in 1926, is employed in Dr. Bloxsom's Air Lock. For a simple and easily available discussion, the reader is referred to a paper by Barach.* Briefly, an increase in atmospheric pressure increases the concentration of molecules in any volume of gas. By increasing the pressure of air in a closed chamber one-sixth above atmospheric, Thünberg thus increased the O_2 molecules in its air (and that of the lungs of a subject within it) by one-sixth more than their former concentration. In the adult subject's lungs containing approximately 3,000 c.c. of air, the resulting increase in content of O_2 would be comparable with inhalation of a breath containing 500 c.c. of air. Reduction to former pressure has the reverse effect. Thus with the chest motionless, the lung volume constant, and a repetition of the pressure cycle twenty times per minute, pulmonary ventilation similar to a tidal air of 500 c.c. $\times$ 20 = 6,000 c.c. minute volume could be imitated.

Dr. Bloxsom† advises cycling of Air Lock pressures 1 to 1.5 times per minute. The atmosphere of 60 per cent O_2 used offers an advantage over that of air; on the other hand, the pressures utilized in the cycle appear to be roughly equivalent to 910 and 810 mm. Hg, which would apply a pressure difference of about one-eighth rather than the one-sixth mentioned above. Obviously, exact calculations are difficult, but the rate at which Air Lock cycling is supposedly effective is so slow that no substitution for the infant's normal ventilation of 500 to 750 c.c. per minute could occur, even were there a relatively large volume of air in the lungs. But if the infant had not breathed, the volume of air in his

*Am. Rev. Tuberc. 42: 586, 1940.

†J. PEDIAT. 37: 311, 1950.

lungs would be nil, and no change in oxygen concentration could occur there. For such reasons one wonders whether the observed effects upon the infant in the Air Lock are not merely those which might occur by placing an infant in an oxygen tent and allowing respiration to begin in these favorable circumstances.

Dr. Bloxsom has stated in earlier papers that a significant amount of oxygen may be absorbed through the skin of the infant in an Air Lock. In this one he suggests the same possibility by mentioning "barospiration through all available pathways." Shaw and Messer* report that in 40 per cent O_2, about 125 c.c. of O_2 is absorbed per square meter of skin per hour. The infant's surface of about 0.25 square meters could thus be permeated by about 30 c.c. of O_2 per hour. Even were the relationship between O_2 partial pressure in the atmosphere and the amount absorbed a linear one (which it does not seem to be), the circumstances in the Air Lock could, at most, perhaps triple the 30 c.c. per hour and provide 90 c.c. per hour. The infant requires 6 to 8 c.c. O_2 per kilogram per minute or $7 \times 3.5 \times 60 = 1{,}500$ c.c. per hour, so that less than one-fifteenth of the O_2 need might be supplied through the skin.

Under headings 2 and 3 of his paper, Dr. Bloxsom advances theoretical arguments which I would challenge but leave for others to answer.

Under heading 4, claims are made for an effect of aerosol therapy which have been disproved by the recent work of Silverman and Andersen, reported to the Society for Pediatric Research in May, 1954.

Finally, in this section, Dr. Bloxsom refers to a paper from our own laboratory as partial evidence that water is absorbed by the pulmonary epithelium from a supersaturated atmosphere. O'Brien, Hansen, and Smith made no such inference. In fact, we were careful to state that our data showed only a reduction in insensible water loss from the lungs of infants in such atmospheres. The statement that "accessory fluid intake of the infant in therapeutic-sized mist appears to be of little importance" therefore seems much too sweeping, and, one fears, likely to lead to harm in the clinical care of infants, if taken at its face value. The same criticism applies to much of this paper.

Discussion by Dr. Virginia Apgar, New York City:

Dr. Bloxsom's concern over the problem of abnormal ventilation is well founded. However, his recognition of the part played by analgesics and anesthetics in reducing infant mortality is not borne out by the depressant drugs given to the eclamptic mother as listed in Table I.

The fortunate and dramatic improvement in full-term infant mortality from 1949 to 1952 (what happened in 1950 and 1951?) in the St. Vincent's Hospital suggests that the infants previously were given negligent care and that oxygen therapy was almost unknown. The statistics for the premature infant mortality cannot be analyzed for significance without more data than are presented by Bloxsom and Angelique.* Bloxsom recognized the more favorable weight distribution in 1952 as compared with 1949, but knowledge of sex distribution is also necessary. The occurrence of a few more female infant births than male can cancel out apparent improvement in mortality figures in premature nurseries.†

The improvement of the infant cited in Table I parallels that of a group of infants studied with capillary blood oxygen determinations during the course of the "Anoxia Study" conducted at the Sloane Hospital for Women and the Babies Hospital during the years 1947 and 1948. None had the benefit of processing in the Air Lock and 71 per cent received no

*Am. J. Physiol. 98: 93, 1931.

*Am. J. Obst. & Gynec., March, 1954.

†Silverman, W.: personal communication.

oxygen therapy at any time. This is shown in the accompanying table.

OXYGEN SATURATION AFTER BIRTH

TIME AFTER BIRTH (MIN.)	NO. CASES	MEAN SATURATION (%)	STANDARD DEVIATION	STANDARD ERROR MEAN
0-5	62	22.9	10.63	1.34
5-10	258	42.3	24.11	1.51
10-15	300	70.5	18.39	1.05
15-30	63	81.6	12.84	1.62
30-60	140	81.7	12.86	1.09
60-120	260	94.3	13.52	0.84

From 3 to 7 minutes the oxygen saturations of the infant in Table I fell within one standard deviation from mean values for a larger population. From 9 to 20 minutes the values all fell within two standard deviations, showing that chance alone could account for the figures quoted.

As for the five principles in his summary:

1. Barospiration does not work at the rate of cycling of the Air Lock (Barach; Thünberg; Apgar and Kreiselman).

2. The idea that cuboidal cells are metamorphosed into a flat form, or into any form, is not adhered to by two eminent pathologists in the newborn field, Drs. Edith Potter or J. Edgar Morison. Such evidence as exists points to the persistence of cuboidal cells in alveoli "which abut on the connective tissue beneath the pleura, around the bronchi and blood vessels."*

3. The idea that hyaluronidase, if it can be shown to reach alveoli, will liquefy the cementing substances between alveolar epithelial cells and aid in its flattening is without evidence.

4. The only carefully controlled series of premature infants treated with humidification of Alevaire or of water shows no advantage of any kind in the Alevaire series.†

5. No controlled study has appeared which indicates whether or not penicillin aerosol therapy *without* intramuscular use of antibiotics will decrease the incidence of death from pulmonary infections in the newborn infant.

*Morison: Foetal and Neonatal Pathology, St. Louis, 1952, The C. V. Mosby Co., pp. 126, 128.

†Silverman, W.: in press.

Discussion by Dr. Nicholson J. Eastman, Baltimore:

I am most interested to know that you are planning a discussion of the Bloxsom apparatus, to be published in the JOURNAL, and I wish very much that I could be of some help. However, beginning last November we started a critical study of the Bloxsom apparatus by putting alternate premature and alternate cesarean section babies in the Bloxsom apparatus and the control babies in an Isolette. Although this study has been going on very well, the number of cases observed thus far is not large enough to permit of valid conclusions, and I should prefer not to express a definite opinion about the Bloxsom apparatus until that investigation is completed. It is being conducted, incidentally, by the Department of Pediatrics with our collaboration.

Discussion by Dr. Peter Gruenwald, Brooklyn:

A good many considerations in the paper under discussion are based on concepts of changes in the lining cells of pulmonary alveoli, which are by no means certain to occur. Arguments concerning the presence or absence of epithelial lining cells in the pulmonary alveoli have raged for many years, and are now continuing among those examining the lungs with the electron microscope. By the same token the important role of hyaluronidase in liquefying intercellular cement (it can hardly be intracellular) appears problematic.

It will be very difficult to evaluate the effects of a spray as suggested by Dr. Bloxsom, containing five potentially active ingredients: Triton A-20, sodium bicarbonate, glycerin, hyaluronidase, penicillin. Such composite treatment will not increase our knowledge as long as we have not found out

the effect of each of the substances. In addition, the full effects of a mist of water have not been recognized.

I doubt that the formation of hyaline membranes in the lungs can be construed as an attempt on the part of the lungs to achieve a certain goal. In the first place, these membranes are not present in the *alveoli* in premature infants; second, I am convinced that the significant pathologic lesion in premature infants is a peculiar type of atelectasis which may occur with or without hyaline membranes.

Discussion by Dr. Edith L. Potter, Chicago:

Dr. Bloxsom's recommendations for use of the Air Lock and Alevaire are based on his concept of the lung as a structure lined by cuboidal cells which become plastic through the inhibition of fluid and thus capable of deformation, and that as a result of "pressures" engendered by labor they either flatten out or separate, the bare spaces produced by the latter process causing the deposit of a hyaline membrane for their protection. He also says, "The premature infant's cuboidal cells through labor have the stimuli of pressures but are not mature enough to undergo metamorphosis." He further states that he believes "the intracellular binding cement (hyaluronic acid) also may hinder progressive expansion of the pulmonary alveoli and the separation of the squamous alveolar cells of some infants to provide functioning alveolar sacs."

It is apparent from his description of the development of the lung and the way it expands that the author is neither familiar with the voluminous literature on the development of the lung nor has he studied the development of the lung from actual sections. There are over 150 papers on this subject from which the author selected small portions of three written in 1905, 1920, and 1923 on which to base all his theories. In the thirty years since 1923, when Stewart's paper was written, it has been agreed that alveoli are not present in very early fetal life at the time the pulmonary tree is lined by cuboidal cells, and that when alveoli are formed, they are at no stage lined by cuboidal cells, but are composed largely of capillaries with interspersed interstitial cells from the time the first alveoli appear in mid-fetal life. Whatever "pressures" are thought to make a difference in the structure of the lung during passage through the birth canal are unknown to me. Except for size of lumens of alveoli and alveolar ducts there are no differences in the histologic structure of the lungs of the fetus before and during birth and the first hours after birth. The concept that alveoli are lined by epithelial cells that must undergo a change during labor, or at any other time, in order that they can flatten out is untenable. Equally without foundation is the concept that the cells pull apart, leaving a raw surface that becomes protected by hyalin. Furthermore, the statement that hyaluronidase in Alevaire "offsets the binding action of hyaluronic acid between the low cuboidal cells before they become flattened epithelial cells" seems to imply that these cells need to separate before the infant can breathe, and, as has just been stated, this does not occur. If the value of the Air Lock and Alevaire are to be assessed in view of the author's statements of what they do to the infant's lungs, the conclusion must be drawn that their value is minimal.

Discussion by Dr. A. Ashley Weech, Cincinnati:

You have asked me to comment on Dr. Bloxsom's paper from a statistical point of view. I am happy to comply.

Death rates in the St. Joseph's Maternity Hospital (Houston) for both term and premature infants in 1949 are compared with the rates in 1952. In 1949 the Air Lock was not in use; in 1952 "five Air Locks were widely used." We shall first examine the

data for term infants. Dr. Bloxsom states that in 1949 there were 5,918 term infants delivered with thirty-seven deaths; that in 1952 the data showed 5,702 deliveries with twenty-one infant deaths. Arranged in a contingency table these figures appear as follows:

Term Infants	*Survived*	*Died*	*Total*
1949	5,881	37	5,918
1952	5,681	21	5,702
Total	11,562	58	11,620

The value of chi square computed from this table is 3.86, a figure corresponding almost exactly to a probability integral of 0.05. The odds that the results of 1952 are different from those of 1949 are about 19 out of 20. Stated the other way, the chances are 1 in 20 that the difference in fatality rates is purely fortuitous.

The results for premature infants can again be arranged conveniently in a contingency table as follows:

Prematures	*Survived*	*Died*	*Total*
1949	293	84	377
1952	384	68	452
Total	677	152	829

Chi square computed from this table has a value of 7.19 which is somewhat higher than that required for the 1 per cent level of significance (6.64). The odds are, therefore, less than 1 in 100 that this difference could have resulted from fortuitous circumstances alone.

Having presented the foregoing computations, it is pertinent to point out that the methods of statistics can never do more than define the chances that differences between two sets of data under comparison are not the result of fortuitous sampling. They can never establish a cause-and-effect relationship. The conclusion that the Air Lock was responsible for the improved survival rates must be made by an investigator who with conscientiousness has examined every other possible cause of differences between 1949 and 1952. Comparison of results in one year with those in another is always hazardous. No data are given in Bloxsom's paper to permit assessment of such possibly additional factors of importance in determining differences in survival rates such as nursing hours available per patient, medical resident hours available per patient, epidemics of Salmonella or other infections, etc. Without a detached attitude in the attempt to evaluate all such possible causes of differences, conclusions emanating from chi-square computations rest on a precarious basis.

Discussion by Dr. Joseph B. Miller, Mobile, Alabama:

My experiences with the Air Lock extend over a four-year period. All four of the local hospitals have Air Locks, and two of the hospitals have two Air Locks. I have also canvassed the opinions of local pediatricians, obstetricians, and nursery personnel, and there is almost unanimous approval of its value *in certain types of cases.* I share their favorable opinion to this extent.

Interestingly, there was a definite pattern in these opinions. The most favorable opinions came from those who had used it most frequently and over the longest period of time, had studied it most thoroughly, and had observed most closely its effects on all types of respiratory problem cases. Yet even these limited their favorable opinions to a small group of cases. The men least impressed with its value were the ones who had just completed their residency training, had been taught that its theoretical basis was questionable, and had had little experience with it. No one had ever seen it do actual harm, although all were familiar with the theoretical possibility of increasing a pulmonary or intracranial hemorrhage by its pumping action.

There is a great tendency to condemn anything that cannot be immediately "proved" by animal experiments or statistical analysis. Of course, healthy skepticism is the backbone of science. However, this skep-

ticism, plus the unusual and perhaps mystical theories of the rationale of the Air Lock, has resulted in attacks that have so beclouded the issue and confused the profession that we have lost sight of the one question that matters, namely, is it of any *clinical* value?

I have seen a few infants resuscitated by the Air Lock who had failed to initiate respiration after pharyngeal aspiration, use of the Emerson resuscitator, classical artificial respiration, injection of stimulants, and tracheal intubation with suction and intermittent oxygen insufflation directly into the trachea. These have chiefly been limp, narcotized infants or infants with intrauterine anoxia, immaturity, precipitate deliveries, or cesarean sections, rather than infants vigorously retracting from atelectasis. I have also seen infants whose respirations have been established, with or without the Air Lock, who later became apneic and were restored to normal respiration by the Air Lock after all other methods had failed. (Conversely, I have seen tracheal intubation work when the Air Lock failed.) The infants benefited were usually the limp type, although they were occasionally normal small premature infants who had simply stopped breathing reflexly, due to a drop of mucus in the pharynx or larynx. Simple aspiration should remove the mucus and remedy the situation, but an occasional baby will still not breathe, and I have seen some of these respond immediately to the Air Lock who had failed to respond to all other methods. Furthermore, I have had this happen several times in the same infant. When a single resuscitational measure is repeatedly successful in the same infant after all other methods have repeatedly failed, one does not need statistics or animal experiments to be convinced of its value, at least for this particular patient. Admittedly, these cases are few, but they are important.

In my experience, the Air Lock alone has not been a great help in primary atelectasis, in secondary atelectasis due to retained secretions or aspirated amniotic fluid, or in so-called pulmonary hyaline membrane disease.

Some infants seem to be irritated into breathing by the mounting positive pressure, but more often the stimulus to breathe accompanies the sudden *release* of pressure. Every time the relief valve "pops off," the apneic baby jumps and takes a single gasping respiration. This often keeps him pink and alive until the narcosis wears off and he begins to breathe more regularly on his own. It is as though the Air Lock were a mechanical nurse who thumped his feet sharply and regularly, although, of course, the effect is much better than one could obtain by thumping since it is received diffusely, by the entire body.

It is important to accept the Air Lock as only one of many resuscitative procedures. The pediatrician who is experienced in resuscitation will use the Air Lock judiciously, selecting it only for types of cases in which it is beneficial and not using it as a panacea. He must *always* clean the airway of secretions before introducing the infant into the Air Lock, and keep *constant observation* to determine if repeated suctioning or other procedures are indicated. Good pediatric care and judgment are the essential ingredients of successful resuscitation. It cannot be left to any type of robot. The practice of placing the baby immediately in the Air Lock to shift responsibility for resuscitation to a mechanical instrument is to be condemned.

Alevaire, on the other hand, exerts its chief effect on infants with atelectasis or retained mucus or amniotic fluid.* Its effectiveness lies in its ability to lower the surface tension of sticky mucosal surfaces and liquefy retained secretions. The infant whose lungs are blocked or imperfectly expanded will usually fight hard for oxygen, vigorously retracting with each inspiration. When given Alev-

*Miller, J. B., and Boyer, E. H.: J. PEDIAT. 40: 767, 1952.

aire *in a dense fog,* the secretions will usually become thin, and he will gradually expand his lungs and finally breathe normally. It is difficult to diagnose atelectasis clinically in an infant who is limp from narcosis, intrauterine anoxia, or injury, as he will not have the strength to retract and struggle for air, and indeed may not breathe at all. Thus, the combination of limpness and atelectasis is doubly dangerous. It is this type of infant for whom the simultaneous combination of Air Lock and Alevaire will be most useful. It is admittedly not the most frequent type of problem seen, and might not affect mortality statistics markedly, but each case represents one human life worth saving.

Alevaire, to be effective, must be *started early and given long.* It should be administered prophylactically to premature infants, cesarean section infants, and all other infants predisposed to abnormal pulmonary ventilation, immediately after birth and continued a few hours until it becomes apparent whether or not the infant is going to develop respiratory trouble. Those who develop difficulty have been given Alevaire in time to help. Those who do not can simply have it discontinued.

Aerosols are deposited in the lungs too slowly to wait until the infant is nearly terminal or his secretions partially dried out into plugs or membranes. For the same reason, Alevaire must be administered with good nebulizers, in proper droplet size range, in a *dense* floating fog, not a thin barely visible mist nor a drenching rain. Also it should never be used in an Isolette incubator, as the forced air circulation draws the mist out almost as fast as it can be formed, and a therapeutic concentration of aerosol droplets is difficult to obtain.

Since early administration is of such importance it is best to start with it immediately in the Air Lock rather than take a chance on the Air Lock alone over a period of hours. A certain amount of drying out of the infant can occur, if he has to remain in the Air Lock over a long period of time. One of my colleagues once had an infant that had to be shifted to an incubator repeatedly for humidification, then back to the Air Lock for failing respiration.

The value of adequate humidity in preventing drying out of retained secretions or amniotic fluid is now well known. Alevaire provides a more intense form of humidity than can possibly be obtained with plain water mists, and its mucous-liquefying effect on newborn infants, older children, and adults is attested by a rapidly growing body of literature. This mucous-liquefying effect can easily be demonstrated and the reduction in surface tension measured in the laboratory and in adults who expectorate their sputum. Infants do not expectorate, and it is virtually impossible to obtain sufficient neonatal sputum to measure surface tension changes during Alevaire exposure. It is necessary to use older children or adults with bronchiectasis or similar conditions for this study, and I urge all doubters to make such a study. The measurable reduction in sputum viscosity, the new-found ability to raise secretions with ease, the emptying out of these secretions from a chronically loaded bronchial tree, and the degree of relief obtained are all very obvious and striking.*

It is well known that the initial force required to expand the lung is greater than the force required for respiration after the lung has once expanded. This is due to the necessity of overcoming the initial high surface tension. Gruenwald has shown that the force required to expand the lungs of stillborn infants is markedly reduced after the introduction of a detergent.†

Alevaire deposits liquid droplets in the lungs, and is therefore of value in preventing excessive weight loss and

*Miller, J. B., and others: Alevaire Inhalation for Eliminating Secretions in Asthma, Sinusitis, Bronchitis, and Bronchiectasis of Adults, Ann. Allergy, in press.

†Gruenwald: Am. J. Obst. & Gynec. 53: 996, 1947.

dehydration due to water loss from the lungs in the first hours of life* It has also been shown to diminish the formation of pulmonary hyaline membranes in animals.† Babies who require the Air Lock for resuscitation are just the types who are most susceptible to respiratory obstruction and pulmonary hyaline membranes and are most in need of adequate fluid balance. I can see no possible harm, and can visualize much possible good, that can come from combining these two procedures for these specific types of cases.

Alevaire is designed to have a maximum depositing effect on aerosol droplets, as well as a mucolytic effect once the droplets are deposited within the lungs. It carries all compatible aerosol medications into the lungs better than if they were simply dissolved in water, glycerin, propylene glycol, buffer solutions, or any other known solutions. It therefore serves as an ideal vehicle for hyaluronidase or almost any other substance one would wish to deposit in the lungs. I have had a little experience with hyaluronidase aerosols, but have as yet observed neither benefit nor harm from their use. Their freedom from side effects cannot be stated about any of the other enzymes commercially available at present.

However, the principle of introducing detergents, enzymes, and other medications by this route for obstructive respiratory conditions is sound, and further progress may be expected in this field in the near future. For example, I have had two cases of severely retracting newborn infants who were almost completely relieved within three minutes after inhaling two or three whiffs of 1:200 Isuprel, a powerful bronchodilator. This does not happen often as I have tried it in many cases without success. It has been harmless in this dosage and in fact appears to strengthen cardiac action, but more study is required to determine its true value and safe dosage. Another example is the inhalation of Levophed, a peripheral vasoconstrictor, for elevating blood pressure quickly for newborn infants in shock. It is a rational approach as the molecule has been stated to be readily absorbed across the mucosa, but, again, more study is required. A lyophilized papain is currently being studied as an aerosol, and may prove to be less toxic than other available enzymes. I have had marked preliminary success in laboratory studies with new antifoaming agents, which may prove useful in clinical pulmonary edema. I am continuing to work with these and other aerosols, and feel that this is a field that has much to offer for the future.

The problem of respiratory difficulties in the newborn period is of too great a magnitude and the therapeutic tools too few to waste our time quibbling about theories. Patients should certainly never be deprived of any practical treatment because of as yet unproved dogma or belief as to its mode of action. Every new approach should be thoroughly tested clinically, and whether empirical or purely scientific, we should use what works, and discard what does not. Let us learn the uses, regardless how limited, of whatever tools we have, avoid slavish adherence to one instrument, theory, or therapeutic procedure, use all things available and combine them if necessary, and continue to work for more and better treatments in the future.

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*O'Brien, Donough, Hansen, J. D. L., and Smith, C. A.: Pediatrics **13**: 126, 1954.

†Bruns, P. D., and Shields, L. V.: Am. J. Obst. & Gynec. **67**: 1224, 1954.

PROGRESSIVE HYPOTHALAMIC DYSFUNCTION

Observations on the Effects of Primary Neoplastic Destruction of the Hypothalamus

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FROM the standpoint of evolution, the hypothalamus is an ancient structure, and, like the kidney, its functions are related to the more basic biologic phenomena. In spite of the obvious importance of such a structure, the average physician retains only a cursory knowledge of its anatomy and physiology and consequently has a rather limited understanding of the clinical reflections of its disease processes.

The purpose of this paper is to present an interesting and unusual case of progressive neoplastic destruction of the hypothalamus which demonstrated in an instructive fashion several of the less commonly known hypothalamic functional relationships.

CASE REPORT

C. D., No. 52-59181, a 2-year-old white male, was followed at Children's Hospital from his eighth month of life. During this sixteen-month period he was admitted five times.

He was the product of a normal, full-term, third pregnancy and the labor and delivery were uncomplicated. The birth weight was 6 pounds 4 ounces. A review of the family history revealed nothing unusual and, prior to the patient's first admission to the hospital, he was thought to be a normal child in every respect.

First Admission.—The child was first seen at Children's Hospital on July 11, 1951, at the age of 8 months. This admission was prompted by onset and progression of weight loss associated with "large, oily, foul-smelling stools." The weight at that time was 15 pounds 12 ounces, length 73 cm., and occipitofrontal circumference 44.5 cm. He was undernourished and appeared to be not acutely ill. His abdomen was somewhat distended, but no organs were palpable. The remainder of the examination, including a complete neurological survey, was within normal limits. His blood cytology and urine examination were within normal limits of variability, and the serologic test for syphilis was negative. A stool film digestion indicated the presence of trypsin, and duodenal drainage revealed 437 units of this enzyme per cubic centimeter. An upper gastrointestinal series was reported as showing pylorospasm which was relieved by instillation of procaine solution into the stomach.

A Shigella-like organism was cultured from the stools and, though this organism was biochemically and culturally Shigella, it failed to type out with specific Shigella antiserum. The boy improved on Chloromycetin and diet therapy and was discharged with a tentative diagnosis of celiac disease. The enteric organism disappeared under Chloromycetin therapy.

Second Admission.—The patient was readmitted on Aug. 20, 1951, at 9 months of age (Fig. 1) because of undue enlargement of his penis, unusual strength, and continued presence of greenish, oily, foul-smelling stools. At that time his length was 73 cm., weight 16 pounds 15 ounces, and occip-

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itofrontal circumference 45 cm. The examination was essentially unchanged over his previous admission except for prominence of the skeletal muscles and a rather large penis. The testes were felt to be normal in size and no evidence of axillary or pubic hair was noted. His strength and muscle development were so unusual during this admission that he could climb the crib side bars and use of a crib net became imperative.

Third Admission.—The patient was again readmitted on Feb. 29, 1952, at the age of 15 months (Fig. 2) because of an acute infection (rubella). At that time he was 79 cm. in length and the weight was 17 pounds 7 ounces. The occipitofrontal circumference was recorded at 47 cm. and it was noted

Fig. 1.—C. D. at 9 months of age, during his second hospital admission. Note prominent musculature and large external genitals.

X-ray examination of the wrists showed no evidence of either delayed or accelerated maturation. Intravenous pyelograms were negative, and a skull film demonstrated no evidence of pathology. Routine blood counts and urinalyses were normal. The nonprotein nitrogen was 30 mg. per cent, serum sodium 134 meq. per liter, serum chlorides 107.9 meq. per liter, and serum potassium 5.7 meq. per liter. The carbon dioxide capacity of the serum was 24 meq. per liter. A Thorn test using ACTH was within normal range, and 17-ketosteroid excretion was 0.5 mg. per day. He was discharged with a diagnosis of possible tumor of the adrenal gland with virilism.

that the boy was somewhat emaciated, having very little subcutaneous fat. The precocious strength and muscular development noted previously were much less prominent at this time. He was weak and not nearly so active or happy as before. During this admission, the patient was seen by a consultant from the Metabolic Institute of Oakland, California, who felt that the main difficulty was related to intestinal absorption.

A pneumoencephalogram was done and was reported to be within normal range. There was no evidence of in-

creased intracranial pressure and a complete gastrointestinal series was negative save for a suggestion of mild duodenal obstruction. A lymph node biopsy revealed only mild reactive hyperplasia. The spinal fluid was within normal limits as were urinalyses, Thorn test, and serum cholesterol (190 mg. per cent). The blood smear showed a mild hypochromia. The boy was discharged with a diagnosis of rubella and progressive muscular dystrophy (mixed form).

In April, 1952, at the age of 17 months, the patient was seen by a nationally known endocrinologist who felt that the basic difficulty was lipodystrophy and gave a good prognosis.

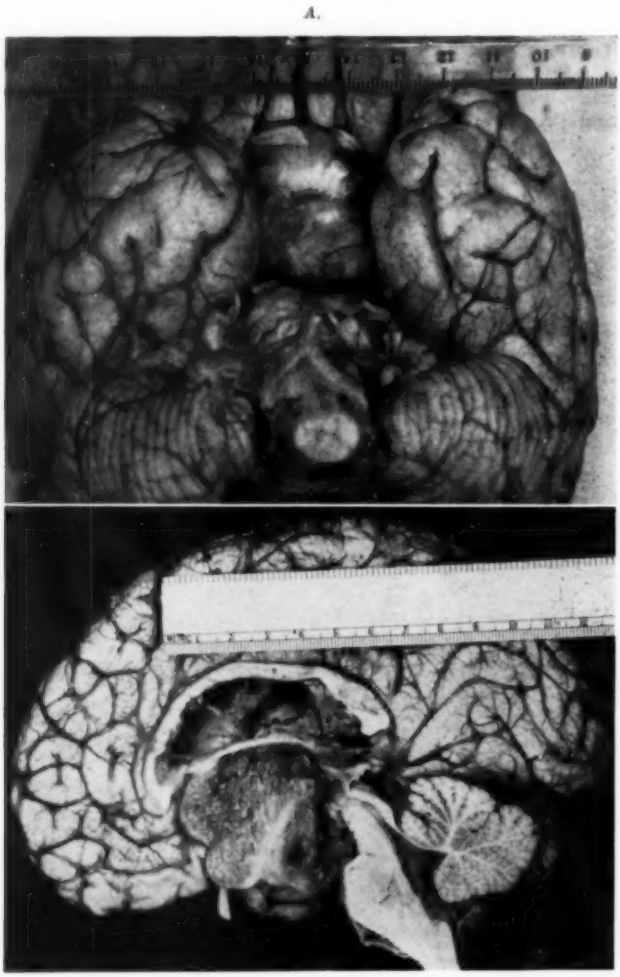
Between April, 1952, and October, 1952, the boy seemed to do fairly well and it is recorded that during that interval he was active and happy. He was noted to crave salty foods, but otherwise was unchanged.

Fourth Admission.—The child was readmitted on Oct. 27, 1952, at the age of 23 months because of an episode of vomiting followed by moderate lethargy. Length was 87.5 cm., weight 17 pounds 9 ounces, and occipitofrontal circumference 51 cm. Examination revealed a rather irritable child with practically no subcutaneous fat, generalized atrophy of the muscular system, and extreme weakness. The genitals were felt to be essentially normal and a neurological examination was negative except for a moderate nuchal rigidity. The spinal fluid was within normal range considering a slightly "bloody tap," and the blood and urine were again normal. He improved and was discharged with a diagnosis of lipodystrophy and mild gastroenteritis.

Final Admission.—On Dec. 9, 1952, the patient was again readmitted at

Fig. 2.—C. D. at 15 months of age, during his third hospital admission. Note the obvious loss of subcutaneous fat.

age of 2 years. Since his previous admission he had not been eating well and had become more emaciated. He was noted to be lethargic at times and had developed severe "temper tantrums." His mother stated that he did not like to have his head touched. On examination he resembled a "little old man." His length was 89 cm., weight 18 pounds 8 ounces, and occipitofrontal circumference 51 cm. The examiner felt that the penis was large and noted a questionable papilledema. The neurological examination was not remarkable.



A.

B.

Fig. 3.—*A*, Inferior surface of the brain. Note the large mass of neoplastic tissue in the floor of the third ventricle and between the optic nerves. *B*, Right half of brain after sagittal section, showing massive neoplasm which fills the third ventricle.

A ventriculogram was done which demonstrated a large tumor mass almost completely filling and grossly dilating the third ventricle. The blood sugar was 79 mg. per cent (fasting).

A craniotomy was done and a Torkildsen drainage instituted. The postoperative course was stormy and the patient died on Jan. 2, 1953. Autopsy permission was granted.

replaced much of the hypothalamic tissue.

The microscopic examination (Fig. 4) identified the tumor with the ependymoma group. Using Kernohans'

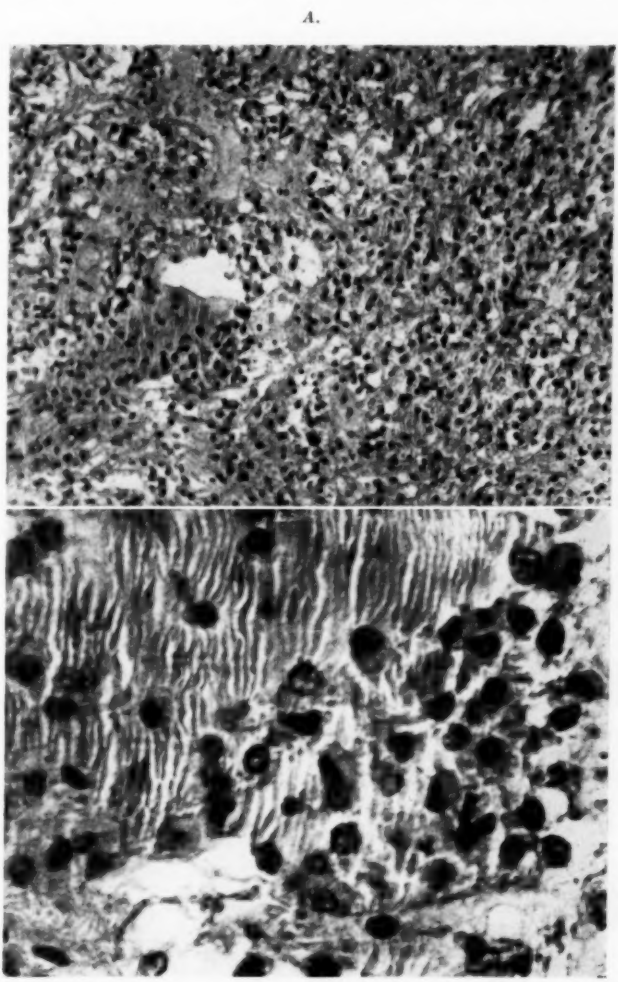


Fig. 4.—*A*, Low-power photomicrograph of tumor, showing general structure. *B*, High-power photomicrograph of tumor, showing the "colloid" stroma.

At autopsy, the tumor (Fig. 3) was demonstrated to be approximately 4.5 cm. in diameter. It filled the third ventricle almost completely and had

classification of the ependymomas this tumor best fits the group of "cellular ependymomas." It does, however, show some mixed characteristics in

that one sees a "colloid" stroma in much of the neoplasm while pseudorosettes are present elsewhere.

DISCUSSION

It is obvious that this paper cannot develop the subject hypothalamic function and malfunction in detail but the case sharply divides itself into four clinical phases, each characterized by a prominent symptom or symptom complex, and one may approach the hypothalamic functional relationships on this basis.

The hypothalamus[1] makes up the floor and lower portion of the lateral walls of the third ventricle. Anteriorly it is limited by the lamina terminalis and posteriorly it includes the mammillary bodies. It is separated from the thalamus, which forms the upper portion of the walls of the third ventricle, by a shallow groove called the sulcus hypothalamus. Four groups of nuclei are included in the hypothalamus: an anterior, middle, a lateral, and a posterior group. Five clinical syndromes have been described which are attributable to lesions of these nuclei:

1. Hypothermia—posterior group.
2. Hypersomnia—posterior group.
3. Adiposogenital—tuber cinereum and lateral group.
4. Diabetes insipidus—anterior group.
5. Autonomic epilepsy—combined lesions.

Kennedy[2] summarized hypothalamic tumors and their symptoms in the following way:

Tumors:

Most common:	Suprasellar craniopharyngioma
	Glioma of optic chiasm
Less common:	Suprasellar meningiomas
	Hypophysial adenomas
	Gliomas and ependymomas
	Pineal and midbrain tumors

Symptoms:

Most common:	Obesity
	Sexual disorders
	Diabetes insipidus
	Glycosuria
	Sleep disturbances
Less common:	Hyperpyrexia
	Blood diseases
	Alimentary ulceration
	Emotional disturbances

These major well-known clinical syndromes are not always so definite, however, and bizarre pictures may be seen when they are mixed or combined.

As previously mentioned, our case presented symptomatology which divides itself into four phases.

Phase I. Gastrointestinal Phase.—The first clinical phase was characterized by bowel disturbance in the form of large, foul-smelling stools which were oily in character.

There is reliable experimental evidence[3] to support the existence of a sympathetic center in the hypothalamus. This center is apparently located in the lateral hypothalamus and mammillary body regions. An adequate stimulation of the hypothalamus is known to be followed by inhibition of peristalsis and diminished tone of the musculature of the stomach and intestines as well as increase in the mucus content of gastric juice and a decrease in its rate of flow. Hypothalamic effects on the function of the gastrointestinal tract are demonstrable in many ways. Clinically it has been noted that lesions in the central nervous system are often associated with gastrointestinal hemorrhage and erosion (Cushing's ulcer). The central nervous system lesions most frequently associated with this are hypothalamic though it has also been noted with lesions of the midbrain, pons, and spinal cord. One-third of all experimental hypothalamic lesions

are associated with gastrointestinal hemorrhage and erosion. It has been postulated that such gastrointestinal disturbance is produced by an overactive sympathetic center in the hypothalamus resulting from irritation by adjacent lesions. Knowing the relationship of the sympathetic nervous system to glandular and smooth muscle function and recognizing the existence of a sympathetic center in the hypothalamus, the initial diarrhea and pyloric spasm seen in the case history could perhaps be attributed to a lesion of hypothalamic location.

Phase II. Virilism.—The second clinical phase was characterized by the presence of a large penis and unusual strength.

Prior to 1930, dysfunction or anatomic disease of the pineal body was commonly held responsible for cases of precocious puberty not related to the endocrine glands, such as the adrenal and pituitary. This incrimination of the pineal was, however, later shown (Bailey and Horrax, 1928[5]) to be fallacious and the real cause of the precocious puberty was related to invasion of the pineal tumors into the hypothalamus. This interpretation was supported by such cases as those reported by Huyer and associates[4] in which a tumor involving mammillary bodies and tuber cinereum produced precocious puberty in the face of normal pineal, pituitary, and adrenal glands. Many authors have since demonstrated the relationship of the hypothalamus (particularly the posterior group of nuclei) to precocious puberty.[5, 6, 7] Known relationships, both nervous and vascular, between the hypothalamus and the pituitary gland are not thoroughly worked out, and it may be that precocious puberty in hypothalamic diseases is in some way produced through such a relationship.

Phase III. Lipodystrophy Phase.—The third phase of the clinical course of the case was characterized by loss of subcutaneous fat.

The hypothalamus is definitely concerned in fat metabolism and here, again, the exact relationship of the pituitary gland is not known. It is known, however, that both the pituitary and the hypothalamus can individually influence fat metabolism. As early as 1921 experimental evidence of the role of the hypothalamus was available. In that year Bailey and Brenner observed that large experimental lesions of the hypothalamus involving the tuber cinereum resulted in cachexia and genital atrophy. Silver nitrate injuries to the tuber cinereum region in dogs produces adiposity and genital atrophy as was shown by Grafe and Grunthal in 1931. Since that time many experimenters have been able to produce aberrations in fat metabolism with large lesions of the tuber cinereum region which did not involve the pituitary. Small lesions in the hypothalamus rarely disturb fat metabolism.

It is interesting to note the work of Gildea and Man[8] in this regard. They observed that patients with hypothalamic disorders generally had elevated serum lipoids whereas patients with diseases of the pituitary gland did not.

Phase IV. Neuropathologic Phase.—In the fourth phase of the patient's clinical course the signs and symptoms of hydrocephalus and increased intracranial pressure were obvious. The growth of the tumor simply obstructed the foramina of Monro and resulted in distention of the lateral ventricles.

Analysis of the Case.—It is our opinion that the tumor began as a small nidus in the floor of the third ventricle in the region of the mammillary bodies. Here as a small lesion it irritated the central cells of the sympathetic nervous system, causing changes in the functional balance of the gastrointestinal system and producing the celiac-like symptoms as well as the pyloric spasm. As the tumor grew, it extended slowly along the third ventricle floor. It produced progressive destruction in the mammillary bodies and caudad portion of the hypothalamus, resulting in virilism or a surge of the organism in that direction. As the growth proceeded, the tuber cinereum was involved and fat metabolism was affected. The tumor then grew toward the line of least resistance (the space of the third ventricle) and eventually came to block the foramina of Monro, resulting in hydrocephalus with increased intracranial pressure and, finally, death.

CONCLUSION AND SUMMARY

A case of hypothalamic brain tumor in the pediatric age group is presented which demonstrates the bizarre clinical picture possible with tumors or disease processes involving that site. Some of the important related functions of the hypothalamus are reviewed with regards to manifestations shown by this case, and an analysis of the pathologic physiology is made considering the direction and results of the tumor's growth.

It is felt that a more complete knowledge of anatomy and physiology of some of the body's more remote but important regions can perhaps help in earlier diagnosis and treatment of such problem cases.

Photography is by Mr. I. S. Stephens, M.T.

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SUDDEN DEATH IN INFANTS

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THE problem of sudden death in infants and young children is often quite discouraging to physicians, and it becomes increasingly so, when, after examination of the body, there is no obvious evidence for the cause of death present. This problem is distressing not only to the physician involved but also to the pathologist and family; it also creates an important part of medico-legal work, for all of us are continually seeing this type of death in children. It is quite evident on examination of death certificates that many of the diagnoses which are set forth are placed there simply to satisfy the Bureau of Vital Statistics rather than to indicate the true nature of the death of the patient. It is more evident, however, that we physicians are becoming aware of the inadequacies in our diagnosis and are trying to do something about it.

MATERIAL

Some time ago I discussed the matter with our State Medical Examiner. He pointed out that his office has a number of cases reported to them each year and it might be of interest to review these to see if we could gain some information from what has been reported throughout the State of Virginia. Not having any idea of the total number of cases involved, I picked an arbitrary time interval of eighteen months beginning Jan. 1, 1952, and ending June 30, 1953. I also picked an arbitrary upper limit of four years so that we might include enough cases to make it worth while. Much to my amazement when the records were compiled, I found that there was a total of 1,267 infant deaths. In the same period of time there were 3,600 deaths reported to the Bureau of Vital Statistics for the year 1952 in children 4 years and under. The figure for 1953 is not available, but by taking one-half of the 1952 figure we get an estimated 1,800 more deaths, or an estimated total of 5,400 deaths. Our study then, if these figures are correct, represents only 23 per cent of the total deaths in the State. It is interesting that of the 3,600 deaths for the year 1952, 3,144 of them were in the age group 0 to 1 year and only 456 in the age group 1 through 4. I am sure that many of the former are stillbirths which is a problem of its own and which I am not going to discuss at this time.

Table I shows a breakdown of the total number of cases reported, and it can be seen that by far the greatest number of deaths have occurred in the natural group. In addition, it can be seen that of a total of 130 autopsies performed on this group, 104 were performed on those patients listed as dying of some type of natural death. This represents 14 per cent of

Read before the American Academy of Forensic Sciences in Chicago, Feb. 25, 1954.

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the 729 cases, and it is from this segment that I hoped I could gain the most information.

Table II is a breakdown of the type of diagnoses which were made on those patients dying either from homicide or accidental means. It can be seen with regard to the latter that histories obtained from our group of autopsied cases on which we will spend more time.

By far the greatest number of deaths, 729, occurred in the natural death group. Table III shows a breakdown of the cases of natural death as to age, race, and sex. It

TABLE I. BREAKDOWN OF TOTAL DEATHS OF CHILDREN 4 YEARS AND UNDER, WITH NUMBER OF AUTOPSIES PERFORMED

1. Homicide	13	1. Total number of autopsies	130 (10%)
2. Accidental	296	2. Number of autopsies on accidental deaths	18 (6%)
3. Stillborn	229	3. Number of autopsies on homicidal deaths	8 (75%)
4. Natural	729	4. Number of autopsies on	
Total deaths	1,267	natural deaths	104 (14%)

TABLE II. TYPES OF DIAGNOSES MADE ON HOMICIDE AND ACCIDENTAL DEATHS

Homicide		*Accidental*	
Strangulation	4	Suffocation	84
Fractured skull	2	Burns	73
Drowning	1	Fractured skull	37
Cerebral hemorrhage (traumatic)	1	Head injuries	24
		Drowning	18
Induced labor with catheter	1	Poisoning	17
Exposure	1	Aspiration of foreign body or medicine	5
Suffocation	2	Strangulation	9
Multiple bruises		Others (electric shock,	
Aspiration vomitus	1	accidents unclassified, heat exhaution, etc.)	29
	13		296

TABLE III. BREAKDOWN OF NATURAL DEATHS AS TO AGE, RACE, AND SEX

Age Groups			*Race*	
Not known	5			
4 mo. and under	507 (69%)	86%	White	303 (41%)
4 mo. to 1 yr.	125 (17%)		Negro	424 (57%)
1 to 2 yr.	51		Unknown	2
2 to 3 yr.	22			729
3 to 4 yr.	19		*Sex*	
	729		Male	442 (60%)
			Female	269 (36%)
			Unknown	18
				729

the diagnosis of suffocation was made eighty-four times and strangulation nine times. I want to point out at this time that the histories involved in these ninety-three cases were in many instances quite similar to the

can be seen that the greatest number of deaths occurred in the group of infants 4 months and under. There were 424 Negro infants as opposed to 303 white, and the predominant sex was definitely in favor of the male

over the female, 442 to 269. The commonest diagnoses made on the nonautopsied cases in this group of 729 infants are listed in Table IV.

TABLE IV. MOST COMMON DIAGNOSES OF NATURAL DEATHS OF INFANTS NOT AUTOPSIED

Pneumonia	178 (12 %)
Natural, unknown	82
Prematurity	67
Interstitial pneumonitis	30 (4.8%)
Upper respiratory infection	24
Meningitis	7
Suffocation and asphyxia	20
Gastroenteritis and electrolyte imbalance	9
Marasmus	31
Heart disease (all types)	10

It should be noted, I think, that a large percentage of the diagnoses in this group of nonautopsied cases are some type of infectious process. Pneumonia appears on the list 178 times, interstital pneumonitis 30 times, upper respiratory infection twenty-four times, and meningitis seven times.

The incidence as compared with the over-all incidence in the 729 cases shows more white children in this group as compared with Negro (59 white, 43 Negro), with 57.7 per cent of the children being 4 months and under as compared with 69 per cent for the over-all 729 cases. Looking at the over-all picture of the diagnoses in these 104 cases (Table VI), it can be seen that there is an increase in the diagnosis of interstital pneumonitis, particularly in the 4 months and under group and the group from 4 months to 1 year. In addition, there is a decrease in the number of diagnoses of asphyxia or suffocation. As is to be expected, as the age of the child increases, there is an expected rise in the more generalized types of infection as the cause of death, such as tuberculosis, lobar pneumonia, myocarditis, influenzal meningitis, and meningitis in general.

TABLE V. BREAKDOWN OF AUTOPSIED CASES OF NATURAL DEATHS AS TO AGE, RACE, AND SEX

Age Groups		*Race*	
4 mo. and under	60 (57.7%)	White	59 (57 %)
4 mo. to 1 yr.	24 (23 %)	Negro	43 (41 %)
1 to 2 yr.	8	Unknown	2
2 to 3 yr.	7	*Sex*	
3 to 4 yr.	4	Male	60 (57.7%)
Unknown	1	Female	44 (44.3%)
	104		104

Of these 729 cases 104 were autopsied, and we were able to more closely correlate the clinical findings in these cases with the findings at post-mortem examination since the pathologic examinations in all instances were performed by pathologists and slides were available for review in most of the cases. Table V shows a breakdown of these autopsied cases with regard to age, sex, and color.

I have been interested, as have many others, in the cases diagnosed as interstital pneumonitis. In this material, particularly in regard to the autopsied cases on which we had material for study, the diagnosis was made directly twenty-five times, and in two additional instances the diagnosis of interstitial pneumonitis and mycocarditis was made in two patients listed from age 2 to 3 years. These twenty-seven cases plus five

cases of my own which occurred in the same time interval make a total of thirty-two cases (Table VII). I would like to spend some time with these cases since the subject is one receiving increasing interest.

dren which I have personally autopsied is most unusual. They actually appear to be slightly larger and weigh slightly more than the average child of the same age group. One of the clinicians who has had several of my

TABLE VI. NATURAL DEATHS, AUTOPSIED CASES, DIAGNOSED MADE WITH RELATIONSHIP TO VARIOUS AGE GROUPS

4 mo. and under		*4 mo. to 1 yr.*	
Unknown	5	Interstitial pneumonitis	6
Interstitial pneumonitis	17 (26 %)	Pneumonia	3
Pneumonia	10 (9.5 %)	Unknown	3
Premature	5	Gastroenteritis	3
Asphyxia or suffocation	4	Meningitis	2
Infectious diarrhea	2	Acute infection	1
Marasmus	2	Congenital defects	2
Intestinal obstruction	2	Others	4
Cerebral hemorrhage	2		24
Others	12		
	61	*2 to 3 yr.*	
		Meningitis	3
		Myocarditis and interstitial pneumonitis	2
1 to 2 yr.		Miliary tuberculosis	1
Congenital endocardia fibroelastosis	1	Intestinal obstruction	1
Cardiac failure and hypertrophy	1		7
Meningitis	2	*3 to 4 yr.*	
Interstitial pneumonitis	1	Interstitial pneumonitis	1
Influenza meningitis	1	Unknown	1
Unkown	1	Meningitis	1
Tracheobronchitis and myocarditis	1	Pneumonia and acute heart failure	1
	8		4

TABLE VII. ANALYSIS OF AUTOPSIED CASES OF INTERSTITIAL PNEUMONITIS

4 mo. and under	17
4 mo. to 1 yr.	8
1 to 4 yr.	7
	32

Clinical Findings.—In analyzing the clinical findings in this group of thirty-two infants, a composite picture of all the signs and symptoms can be given. As a matter of fact, it is possible for me to state to the clinician what the autopsy will reveal when the following history is obtained. These children are all well nourished and healthy and usually give no previous history. The strikingly healthy appearance of the children ventured the opinion that, although he felt these children were larger than normal, the fat was slightly softer, and the child, although grossly appearing healthy and large, did not have the usual firm feel to the tissues that other children of the same size have. Of course, this is a clinical impression and it is impossible to say how much significance can be attached to it. It might, however, lead one to suspect a constitutional factor. The vast majority of these children are under 6 months of age. They may or may not give a history of a slight cold. They may or may not have had loose stools twenty-four to forty-eight hours pre-

ceding death. The child when discovered is either lying face down or he may be covered by a blanket or a pillow. The history is often obtained that the child was placed in bed with the parents and they felt that they may have rolled on the child during the night and suffocated him. These children in nearly all instances are either found dead in bed with the parents, or found dead in the crib either when the family get up in the morning, or they are discovered at feeding time. Occasionally it was reported that the child gives a terminal cry, when in apparent health, and suddenly dies. It is also of extreme interest to me that many of the cases in the other groups in this series of natural and accidental deaths, particularly in the cases diagnosed as pneumonia, suffocation, or asphyxia, gave a similar history.

Gross Findings at Autopsy.—Gross examination of these infants reveals them all to be well developed and well nourished. In many instances, as noted above, the children appear to be extremely healthy, fat babies, but the body firmness in some instances does appear to be slightly softer than one would expect for the same type of individual. On opening the abdomen, the abdominal, pleural, and pericardial cavities do not contain noticeably increased amounts of fluid. The thymus is either normal or slightly enlarged. The primary gross feature of the lungs at autopsy appears to be some type of pulmonary edema and congestion. In some instances the entire lung is described as being dark red in color. In other instances, particularly in my own cases, the lungs are either normal in appearance or show patchy areas in which portions of the lung are firmer and have a deeper color than the surrounding lung parenchyma. Sectioning of the lungs, particularly in the areas of gross involvement, reveal them to show congestion and edema. The upper and lower respiratory tracts may or may not show edema of the mucous membranes with some increase in the amount of mucoid content within the lumen. The lymph nodes, particularly the tracheobronchial and abdominal, are slightly enlarged and grossly appear to be congested and to show edema. The liver, spleen, and kidney are frequently noted to be slightly enlarged, but, except for evidence grossly of slight hyperemia and some evidence of congestion, particularly in the liver and spleen, there are no striking features noted on gross examination. None of the adrenals grossly are reported as showing evidence of hemorrhage. Examinations of the brain reveal some edema and mild congestion which varies from case to case.

Microscopic Findings at Autopsy.—The lungs show varying amounts of edema, congestion, hemorrhage, collapse, and cellular infiltration (Figs. 1, 2, and 3). The extent of these changes varies from case to case and from one portion of the lung to the other. In addition, there is congestion and hyperemia of the pulmonary bronchial tree with some evidence in the areas of involvement of cellular infiltration. Many of the bronchi showed desquamation of the lining epithelium. In some there is a fibrillar-staining material with macrophages within the lumen. The alveolar capillaries are engorged, causing, along with edema of the

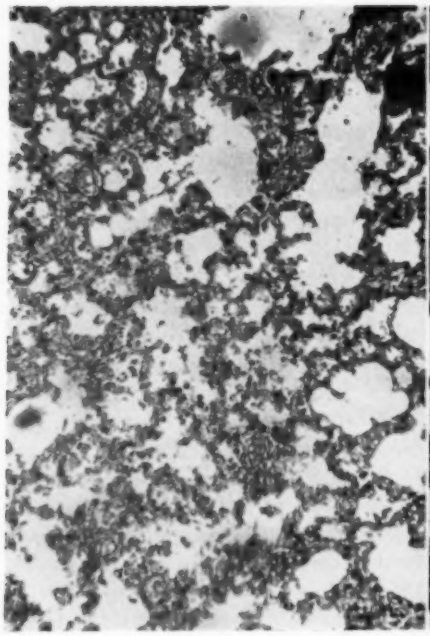

Fig. 1.

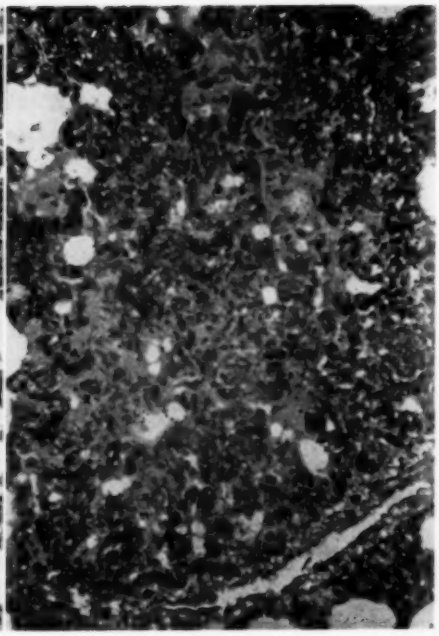

Fig. 2.

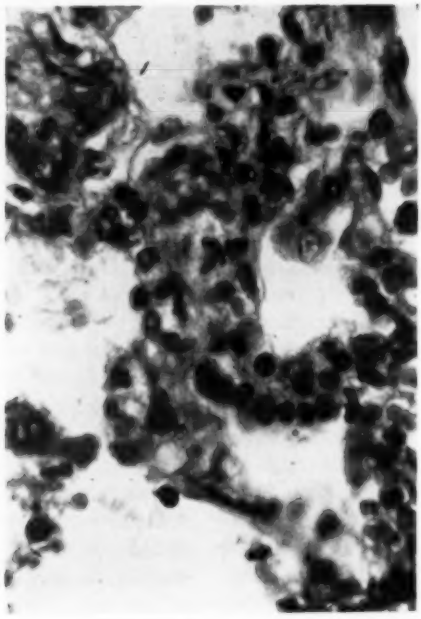

Fig. 3.

Figs. 1 to 3.—Low-, medium-, and high-power fields from a typical lung showing edema, congestion, hemorrhage, collapse, and cellular infiltration. Fig. 3 shows thickening of the alveolar septum with mononuclear cells within the wall and in the lumen.

septum, a noticeable increase in thickness. This usually involves areas adjacent to terminal bronchi in the area of primary pneumonic involvement. Within the thickened septa, hemorrhages are also noted in varying amounts with infiltration by lymphocytes and mononuclear cells with an occasional plasma cell and some macrophages. Within the alveoli there is a picture of edema and infiltration by small numbers of inflammatory cells, particularly macrophages, lymphocytes, and mononuclear cells, with only an occasional polymorphonuclear leukocyte being present. In some sections the areas of involvement appear to be quite large. In other areas the arrangement is quite spotty in character. In only one piece did microscopic examination reveal clumps of bacteria within the lung. There are varying degrees of bronchitis and bronchiolitis. The pleura focally in the areas of involvement sometimes show edema, hyperemia, and occasionally small foci of hemorrhage.

The lymph nodes show evidence of loss of follicular pattern, and in the medullary sinuses of some there are increased numbers of macrophages, lymphocytes, and mononuclear cells (Fig. 4). In addition, some show definite increase in the number of follicles.

The thymus, particularly in Hassall's corpuscles, shows accumulation of cytoplasmic and nuclear debris, and, in addition, edema is fairly prominent (Fig. 5).

Fig. 4.

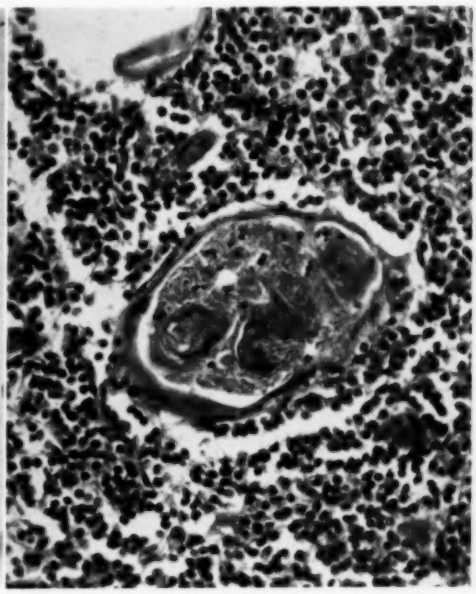

Fig. 5.

Fig. 4.—Low power of a typical lymph node showing loss of follicular pattern with congestion of the medullary portion.

Fig. 5.—Medium power of a thymus showing accumulation of cytoplasmic and nuclear debris in Hassall's corpuscle with separation of the surrounding tissue due to edema.

Sections of the spleen in some cases are not remarkable. In other cases there is a loss of sharp demarcation between the white and red splenic pulp (Fig. 6). Within the red pulp in many instances in the latter cases there are increased numbers of macrophages, mononuclear cells, lymphocytes, eosinophils, and an occasional neutrophilic leukocyte.

The myocardium, except in the two cases associated with an interstitial myocarditis, shows no specific changes. These two cases are difficult to interpret. I am not sure, because all the material was not available, of the significance of these two cases.

In two cases the liver shows evidence of fatty metamorphosis. In other cases there sometimes appears to be a slight increase in the number of round cells in the periportal area, but this, again, is nonspecific. There are varying degrees of congestion present.

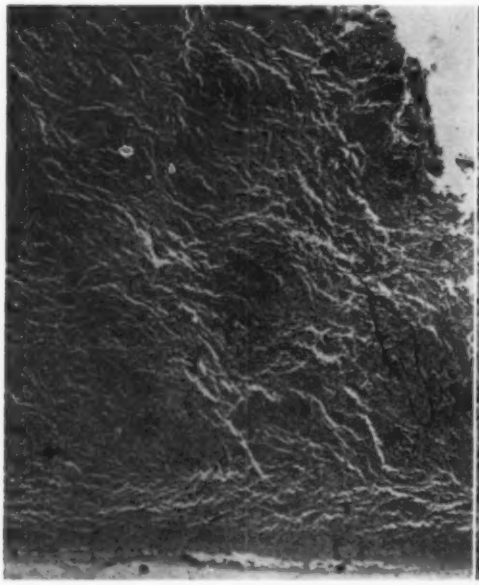

Fig. 6.

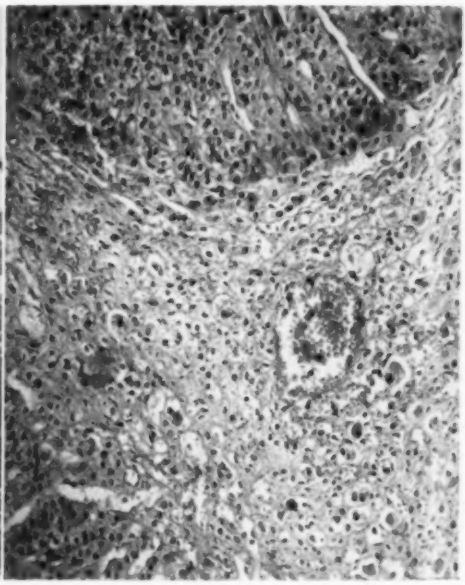

Fig. 7.

Fig. 6.—Low power of a section of spleen to show the loss of demarcation between the red and white splenic pulp which is noted in some cases.

Fig. 7.—Medium power of adrenal medulla to show the congestion which is present. In addition, in some cases, some adjacent areas of focal hemorrhage are also noted.

Examination of the adrenals reveals some hyperemia and in some instances there are small foci of hemorrhage (Fig. 7).

Sections of the brain are negative except for edema and congestion. In one of the cases there is evidence focally of a mild leptomeningeal inflammatory process, to which I can attach no particular importance.

The kidneys are moderately hyperemic, and in one case there is evidence of a focal glomerulitis.

In several cases bacteriologic studies were attempted, but these were not satisfactory. Due to the type of study and the fact that all cases were from hospitals scattered throughout the State, there was not a good bacteriologic study attempted, nor were any reported studies for virus made.

DISCUSSION

We can ask ourselves, at least I have many times, what does all this mean? The most obvious fact is the tremendously high number of infant deaths which have occurred in the State of Virginia in an eighteen-month period. I am in complete accord with the others who have attacked this problem that we can no longer salve our conscience by putting off these children's diagnoses as prematurity, stillbirth, asphyxia, suffocation, or the like. As it was pointed out in a recent article of *The Journal of the American Medical Association,*[1] "It is almost as nonsensible today to make a diagnosis of prematurity in an infant as it is in an adult to state that they have died from old age." In other words, what has been done in many of the cases in this report has been to state that these children simply died from young age. The findings which I have described on the more thoroughly studied cases on which data were available are certainly not new and have been reported by others.[2, 3]

The over-all picture in our cases seems to indicate some type of unknown process which is attacking these children with a rapidity which is quite distressing to say the least. Gruenwald and Jacobi,[4] in analyzing seventy-six cases in 1951 from New York of the same type which I have encountered, spent some time discussing the various possibilities as to the etiology. They point to a virus as the causation of the disease and also point out a significant fact, I think, in that they feel that whatever is the causation of this process it is not necessarily uniformly fatal. Our virus studies, because of the conditions of the study, were not satisfactory, but thorough attempts have been made to isolate a virus from these children and to date this has not been successful.[2, 10] In addition, bacteriologic examinations both before and after death, although in many instances revealing the presence of mixed organisms, have not to anyone's complete satisfaction identified any particular organism as the causation for the sudden death in any one particular infant. The type of histologic pattern in the lungs is seen in so-called viral pneumonitis. On the other hand, in 1941 Mallory and Keefer[5] described tissue reactions in fatal cases of *Streptococcus hemolyticus,* and pointed out changes in the lung not unlike the type of change which I have seen in these patients. In addition, Farber[6] in 1934 described a case of fulminating streptococcus infection in infants as a possible cause of sudden death, with a concomitant interstitial bronchopneumonia which histologically from the description corresponds to the changes which I have noted in the lungs of our infants. It is also of interest that Wolman and associates[7] in 1952 reported five cases of interstitial giant-cell pneumonia in premature infants. They state that the interstitial giant-cell pneumonia is similar to virus pneumonia and plasma cell pneumonia in all respects

except for the presence of giant cells. They feel that perhaps the different reaction which has been described is all quantitative and feel that interstitial giant-cell pneumonia and virus pneumonia represent a single disease entity. In addition, Deamer and Vollinger[8] in discussing a type of interstitial plasma cell pneumonia in premature young infants in Switzerland, remarked that this disease is frequently seen in European countries but so far is undescribed in American literature.

The findings in the other organs, particularly lymph nodes, spleen, thymus, and kidneys, point to some generalized process, possibly infectious in nature, which causes an overwhelming reaction with collapse and death before findings become evident. It may be that the type of individual which I have found in our cases is predisposed to this type of reaction. I am just a little bit depressed over the lack of ability to isolate some type of infectious agent in these cases, particularly where adequate attempts have been made, and to base our impression upon histologic findings, which are somewhat nonspecific in nature. In many instances minimal changes are found with a diagnosis made by inference.

I, and others in the office of the Chief Medical Examiner, do not feel that we have satisfactorily explained the mechanism of death in these infants. I think we can be assured that the diagnoses which have been made of asphyxia, suffocation, prematurity, aspiration, and the like, which have surplanted in many instances the old diagnosis of status thymolymphaticus, are no longer tenable. That fact, of course, is not new to all of us who are dealing with this problem, but I can assure you it is new to many medical examiners as evidenced by the large numbers of such diagnoses which have been presented in these data. I think that it is of extreme interest to note in regard to this change in attitude that the number of diagnoses of interstitial pneumonitis made to the office of the Chief Medical Examiner for the first six months of 1953 equaled the total number of such diagnoses which were forwarded for the entire year in 1952. I personally do not feel that we have come anywhere near solving the problem of the sudden death in these infants. I will not deny that the changes which have been described may be on an infectious basis, but in some twenty years of description no one has been able to satisfactorily isolate an organism. The reactions in the tissue are much too varied and nonspecific, and I feel that other factors must be involved as an underlying mechanism. What they are, I have no idea, and it would be impossible for me, from the type of study which this involves, to state that I do. Some people have tried to explain it on the basis of the Hering-Breuer reflex. Again, I can only say that I do not know. I do not feel, therefore, that I have added anything to the etiology in these infants. I do feel, however, that it is timely from time to time to review our deaths in order to try and gain some impression as to where it may be leading. The high instance of deaths in young infants and young children in our State is not only startling but also rather depressing. One feature which has come out of this study is the fact that we have been able to tell

our medical examiners that children do not usually suffocate, or die from asphyxia. It is reassuring to our own people to know that the statistics pointed out by other workers has been found to be true also in the State of Virginia. From a psychological point of view it is also reassuring for the physician to be able to tell the family that the child did not suffocate, for this implicates neglect and can result in a guilt complex on the part of the family that may last a lifetime. From this study and from the studies of others[2, 3, 9, 10] it is now known that the cause of death in most instances is by natural means. As to the mechanism of death, I think more work needs to be done, and neither I nor the other people in the State who have had an opportunity to see these cases are happy about the post-mortem findings which we have found. I feel it is far better to make a diagnosis of "unknown natural," which tells us we do not know, than it is to state that these children suffocate, strangulate, aspirate vomitus, or die of interstitial pneumonitis.

I feel that larger centers with concentrated pediatric services should attack the problem with new vigor, since isolated cases on a statewide basis are difficult to consolidate into a report pointing to etiology. I do not feel that this report is useless, however, because it is striking that given a history which I have stated, the post-mortem findings are the same, and it makes no difference whether the case is reported from Arlington, Virginia, or Roanoke, Virginia, which is some 550 miles away. That in itself, I think, is significant.

SUMMARY

An analysis has been made as to the causes of death in 1,267 infants and young children 4 years and under, reported to the office of the Chief Medical Examiner in Richmond over an eighteen-month period from Jan. 1, 1952, to July 1, 1953. In the same period there were about 5,400 deaths in the entire State. This study, then, represents about 23 per cent of the total deaths for the same age group.

The greatest number of deaths occurred in the group classified as "unknown natural" (729 cases). One-hundred and four of these cases were autopsied and twenty-seven cases were found to fit into a pattern variously classified as interstitial pneumonitis or overwhelming infection. A closer analysis has been made of these twenty-seven cases plus five additional cases from my own series. A classic symptomatology for these deaths can be given, namely, a child, usually under 6 months, in previous good health, who is found dead in bed. Given that history, it is possible to state what will be the usual autopsy findings. In addition, it was pointed out that many of the unautopsied cases of natural or accidental deaths variously diagnosed as pneumonia, upper respiratory infection, asphyxia, and aspiration of vomitus give the above history and undoubtedly are cases of the same process. The various factors known to date concerning these deaths have been briefly discussed. It is pointed out that in my opinion, and in the opinion of others in the State who have had an opportunity to see or review these cases, that a satisfactory explanation as to the cause of death has not been given.

Finally it is suggested that it is better to sign these children out as cases of "unknown natural" when other known factors can be eliminated than it is to state that these children die from suffocation, prematurity, asphyxia, aspiration of vomitus, or even interstitial pneumonitis. This is important for two suggested reasons. A diagnosis of suffocation carries a psychological impact which may give a family a guilt feeling of neglect lasting a lifetime. It is felt that it is better to make a diagnosis of "unknown natural" in these children, for it suggests that we do not actually know what has killed them. From this it is hoped will come a further search for the fundamental process which is occurring and which kills these infants with such rapidity that it is both startling and distressing.

I am extremely grateful to the Office of the Chief Medical Examiner of Virginia for making this material available for study. I also am grateful to Drs. Geoffrey T. Mann and George Thoma of the Office of the Chief Medical Examiner for help and criticism during the preparation of this paper.

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A STUDY OF HEMOGRAMS IN PREMATURE INFANTS

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THE following study involves a series of hemograms done on 117 premature infants born at the Los Angeles County Hospital, all of whom weighed 1,600 grams or less at birth. Samples were taken at intervals of not less than one week while in the hospital, and also when seen in the outpatient clinic. In all cases the charts were carefully checked to determine the accurate birth weight, and to eliminate any abnormal infant or any hemogram that was done following blood transfusion. All infants were started on supplemental iron* at one month of age (0.6 ml. per day containing 15 mg. of elemental iron).

The hemograms consisted of an erythrocyte count, hemoglobin determination, packed cell volume, leukocyte and differential count. Nearly all of the determinations were made on capillary blood which was obtained by heel puncture. Hemoglobin determinations were done by an oxyhemoglobin method using standardized Newcomer pipettes. Readings were made in a photoelectric colorimeter which was standardized by means of iron determinations and mean corpuscular hemoglobin concentration checks on normal people. Red cell counts were performed for the most part with correction factor pipettes and the usual five 0.2 mm. squares were counted. In a number of the outpatient follow-ups the red counts were done in duplicate, using two pipettes, while the white blood counts and differentials were done in the usual manner. The packed cell volumes were done on capillary blood by the use of the Van Allen hematocrit. Spring clips were used and the specimens were spun for twenty minutes at a relative centrifugal force of approximately 2,000 times gravity.[1, 2] To compare the Van Allen method with the standard Wintrobe procedure for packed cell volumes, ninety-nine determinations were made on fifty-one different individuals, as seen in Table I. In each case a blood sample from venous puncture was placed in suitable anticoagulant, and capillary blood from finger puncture for the Van Allen hematocrit was obtained at the same time. As seen in the data, there is no significant difference between the two methods. In the course of the entire project, however, a number of practical points about the use of the Van Allen hematocrit were noted, the most important being that hematocrits with beveled tips are more suitable than those with flat tips. Both

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Supported in part by a grant from Mead Johnson & Company, Evansville, Indiana.

Presented at Western Society for Pediatric Research, San Francisco, California, Oct. 29, 1953.

*Fer-in-Sol, kindly supplied by Mead Johnson & Company.

are commercially available, but the latter will often leak. Another helpful point in preventing leakage of blood into the oxalate solution is to draw the blood up into the pipette after the column is filled to the 100 placed in the center of the bottom of the cup.

The majority of the samples were obtained in the first fifteen or twenty weeks of life and, hence, statistically, the data are accurate in that period

TABLE I. PACKED CELL VOLUME COMPARISONS (99 COMPARISONS)

WINTROBE	VAN ALLEN
$\bar{x} = 37.94$	$\bar{y} = 37.77$
Standard Deviation = 5.37	Standard Deviation = 5.80
t of diff. = .214	

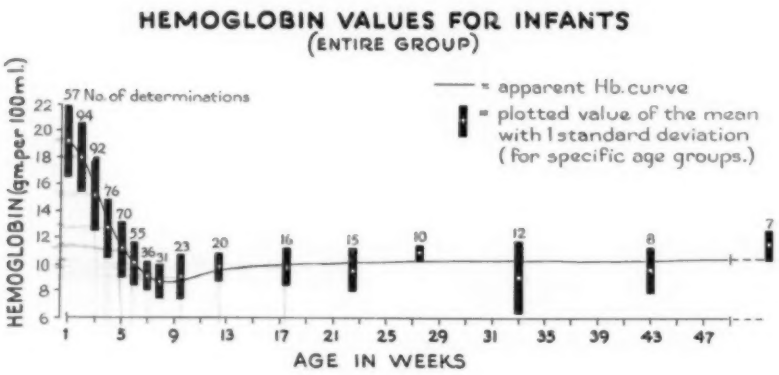

Fig. 1.

TABLE II. HEMOGLOBIN DETERMINATIONS

AGE IN WEEKS	BELOW 1,100 GM.	1,101-1,300 GM.	1,301-1,600 GM.
4	$SE_{\bar{x}} = .52$	$SE_{\bar{x}} = .61$	$SE_{\bar{x}} = .36$
	$\bar{x} = 13.2$	$\bar{x} = 11.4$	$\bar{x} = 13$
8	$SE_{\bar{x}} = .37$	$SE_{\bar{x}} = .43$	$SE_{\bar{x}} = .24$
	$\bar{x} = 8.7$	$x = 8.4$	$\bar{x} = 9$
9-10	$SE_{\bar{x}} = .41$	$SE_{\bar{x}} = .76$	$SE_{\bar{x}} = .57$
	$\bar{x} = 8.3$	$x = 9.4$	$\bar{x} = 9.5$

$SE_{\bar{x}}$ = Standard error of mean.
$\bar{x}$ = Mean.

mark so as to preclude loss of blood in anticoagulant solution. We have found that the metal shields used to hold 15 ml. centrifuge tubes are very satisfactory for spinning down the hematocrits. The hematocrit with the spring tip attached should be only. Although some of the values would appear to be inaccurate, all are included unless there were such technical problems as leakage, breakage, or clotting of blood. The curves of the hemoglobin values for the entire group are seen in Fig. 1, and

for the three weight groups in Fig. 2. In Table II are seen values with the standard error in the different weight groups, at selected ages, and as can be noted, there is little difference in the hemoglobin values in these groups. Curves of the packed cell hemoglobin. For practical purposes, the packed cell volume and hemoglobin curve can be interposed. The corpuscular constants (mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration) were calculated

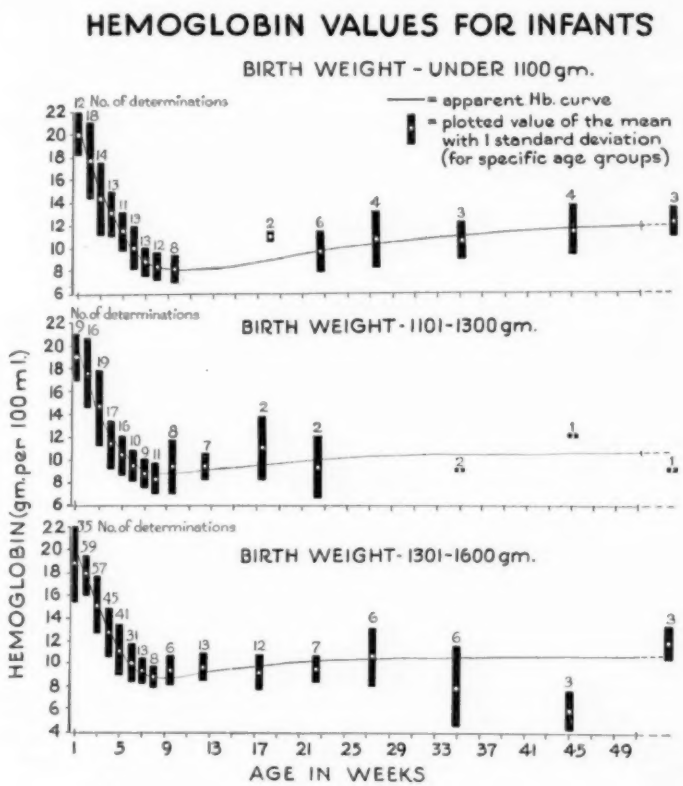
HEMOGLOBIN VALUES FOR INFANTS
BIRTH WEIGHT - UNDER 1100 gm.
No. of determinations
= apparent Hb. curve
= plotted value of the mean with 1 standard deviation (for specific age groups)
BIRTH WEIGHT - 1101-1300 gm.
No. of determinations
BIRTH WEIGHT - 1301-1600 gm.
No. of determinations
HEMOGLOBIN (gm. per 100 ml.)
AGE IN WEEKS

Fig. 2.

volume values and red cell count values for the entire group are similarly shown in Figs. 3 and 4. The lowest values of red cell count, hemoglobin, and packed cell volume are reached at the eighth or ninth week of life. The red count, however, rises much faster after that time than either the packed cell volume or the from the values on the plotted curve, as noted in the diagrams. The results of these determinations are seen in Fig. 5. It is quite apparent that in the early drop of the erythrocyte value the red blood corpuscles are much smaller, on the average, than those at birth, but the hemoglobin concentration of the average cell is

not significantly altered. The individual red blood cells tend to become smaller even beyond this time of minimum count at the eighth and ninth weeks. As has already been emphasized, the great majority of the values in our series are concentrated in the early weeks of life, and little importance is to be given to the curve values after this time.

A tabulation of the white blood counts and the results of differential counts are noted in Table III. The stained blood smear values show only what is generally known, that is, a marked macrocytosis and an apparent

TABLE III. AVERAGE WHITE COUNT AND PERCENTAGE OF LYMPHOCYTES

WEEK	WBC	PER CENT LYMPHOCYTES	NO. COUNTS DONE
1	11,991	46.8	53
2	13,639	52.4	90
3	18,523	55.1	89
4	11,296	59.5	71
5	11,916	62.7	68
6	11,035	65.5	51
7	9,895	65.2	35
8	9,497	64.7	31
9-10	9,007	67.2	19
11-15	11,822	59.0	16

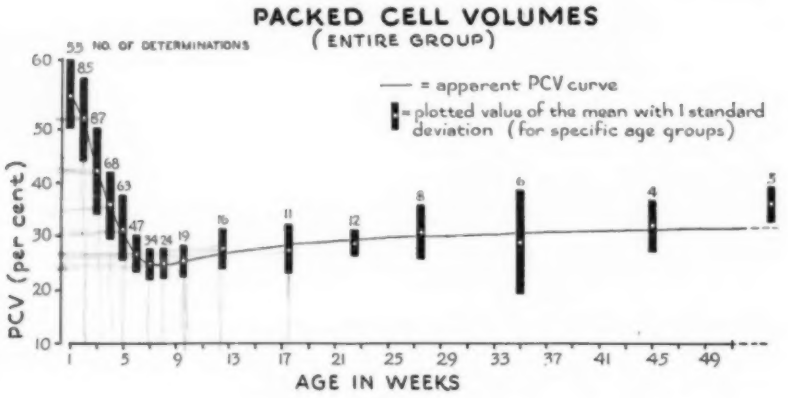
PACKED CELL VOLUMES
(ENTIRE GROUP)
55 NO. OF DETERMINATIONS
= apparent PCV curve
= plotted value of the mean with 1 standard deviation (for specific age groups)
PCV (per cent.)
AGE IN WEEKS

Fig. 3.

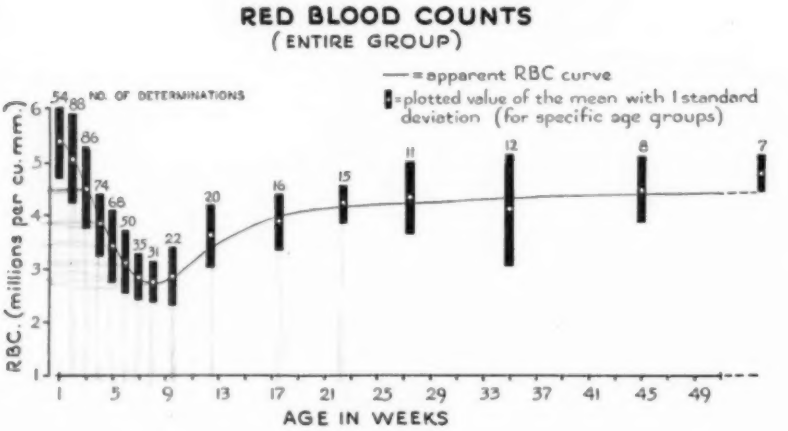
RED BLOOD COUNTS
(ENTIRE GROUP)
= apparent RBC curve
= plotted value of the mean with 1 standard deviation (for specific age groups)
NO. OF DETERMINATIONS
RBC. (millions per cu. mm.)
AGE IN WEEKS

Fig. 4.

crowding of cells in the first week or so of life, and anisocytosis and poikilocytosis developing as the red cell values decrease.

sidered to be statistically significant. The data point out the fact that the cells of the premature infant become smaller, on the average, even beyond

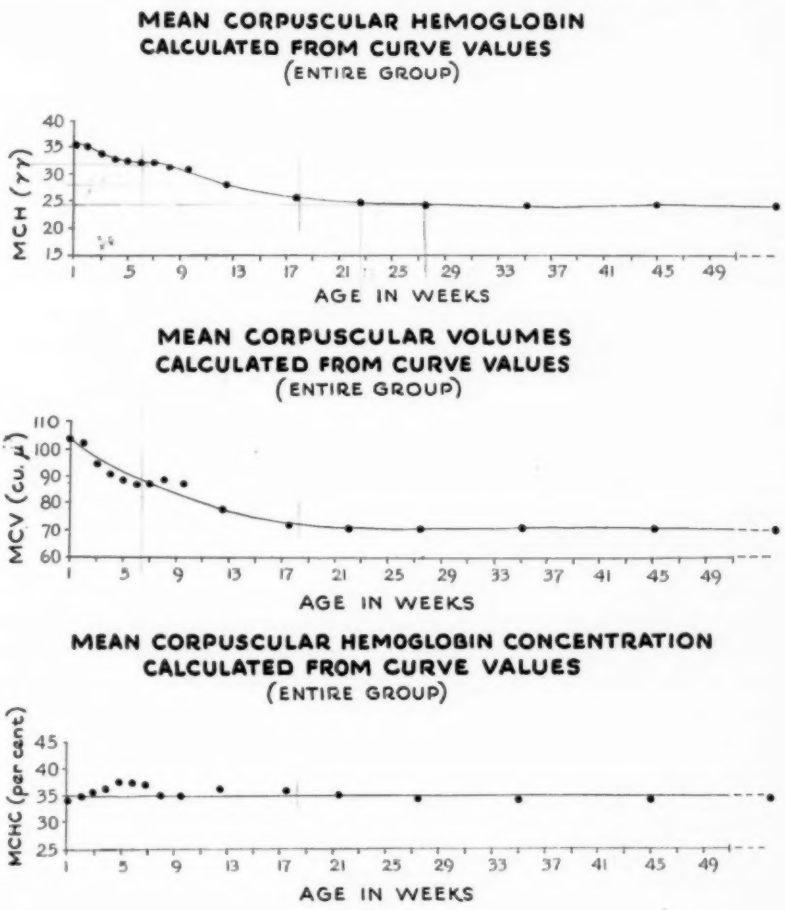

Fig. 5.

SUMMARY

A series of 643 blood counts on 117 premature infants are recorded and tabulated. The majority of these counts are concentrated in the first fifteen to twenty weeks of life and in this range only can they be considered to be statistically significant. The data point out the fact that the cells of the premature infant become smaller, on the average, even beyond the point of minimum erythrocyte values, and also show that the early "anemia of prematurity" is due to an average decrease in number and size of the cell and not in the concentration of hemoglobin in the cell. In other words, the early "anemia of prematurity" is normochromic rather

than hypochromic on the basis of mean corpuscular hemoglobin concentration values.

We wish to extend grateful acknowledgment to Robert F. Woods, Ph.D., for his help with the statistical data.

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THE TREATMENT OF ASCARIS LUMBRICOIDES INFECTIONS WITH PIPERAZINE

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IT WAS demonstrated by Oliver-Gonzalez and associates[1] that the substituted piperazine, 1-diethylcarbamyl-4-methylpiperazine hydrochloride (Hetrazan), is relatively effective against *Ascaris lumbricoides*, the large roundworm of man. Etteldorf and Crawford,[2] Ghanem,[3] and others have confirmed and extended these findings, and there is general agreement that this piperazine compound, when given from three to fifteen days, is effective against Ascaris, although its activity is somewhat irregular when given for less than seven days.

Fayard[4] reported on the treatment of *A. lumbricoides* infections in France with piperazine (diethylenediamine). The active constituent of his syrup was piperazine hexahydrate, which is 44.34 per cent piperazine. Adults were given 1.5 Gm. piperazine (equivalent to 3.5 Gm. piperazine hexahydrate) in the evening and a similar amount the following morning. Fayard reports that approximately 2,000 patients were treated by the cooperating physicians, who reported that 70 to 95 per cent of their patients passed ascarides, beginning usually on the second day of treatment and continuing on the following day. As many as 170 ascarides were passed by individual patients and most of the worms were alive, although dead worms were also noted. Unfortunately post-treatment stool examinations were not routinely done nor were egg counts made, and it is impossible, therefore, to determine the exact cure rate or the over-all worm reduction in this extensive series. No side effects from the piperazine were noted.

Mouriquand and associates[5] gave piperazine to two Ascaris-infected children. One child, who was treated for eight consecutive days, passed eight worms on the eighth day, and the other child, who was treated for two days, passed one worm on the second day of treatment. Post-treatment stool examinations were not reported, and, therefore, the efficacy of the treatment cannot be assessed.

Brown and Sterman[6] reported on the treatment of twenty-three Ascaris-infected children with piperazine citrate. Their dosage was based on the piperazine hexahydrate content of the syrup employed; 1 Gm. daily was given to children weighing between 31 and 60 pounds, and 2 Gm. daily was given to children weighing over 60 pounds. Therapy was continued for three to seven consecutive days. Nineteen of twenty-three patients passed all of their worms as the result of a single course of treatment, based on post-treatment stool examinations for Ascaris eggs. The total egg count reduction of the group was 98 per cent. The authors state that

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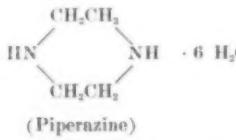
there was no evidence of toxicity or side effects due to the drug.

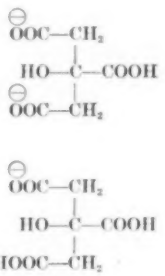
The results reported by the several authors indicate that 1.0 to 3.5 Gm. of piperazine as the hexahydrate are well tolerated, but they do not indicate how many consecutive days' treatment is necessary to achieve a high cure rate. I therefore treated fifty-one Ascaris-infected individuals for two to five consecutive days to determine, if possible, a practical and satisfactory treatment regime.



(Piperazine)

Piperazine Hexahydrate

and



Piperazine Citrates

METHODS

A dilution egg count[7] was made on the stool of each patient before treatment. Two to three weeks after the completion of therapy, a zinc sulfate flotation[8] examination was done on a stool from each child, and if Ascaris eggs were present, an egg count was made.

The piperazine citrate used in this study was supplied as an orange-flavored syrup, each cubic centimeter of which contained 100 mg. equivalent of piperazine hexahydrate. Accompanying are formulas for piperazine hexahydrate and for the two piperazine citrates probably present in by far the greatest amount in the syrup. A teaspoon, which held a measured 5 c.c., was presented to each child. Their schoolteacher administered the piperazine citrate syrup and thus assured that each dose was taken and that the correct amount was given. The syrup was administered at 8:30 A.M., when the children arrived at school, and again at 3:30 P.M., just before they left school. Thus, in general, they received the drug approximately one and one-half hours after breakfast and three hours after lunch. No special dietary regime was suggested, there was no pretreatment fasting, and no purgatives were employed. The pleasant-flavored syrup was readily accepted by the children. None of the patients complained of side effects from the drug, many of them walked considerable distances to and from school, and none of them interrupted their course of therapy. The dosage of piperazine citrate was the same as that employed by Brown and Sterman (Table I).

RESULTS

Forty-six of the fifty-one Ascaris-infected children treated with piperazine citrate passed all of their worms as the result of a single two- to five-day course of treatment. This is a cure rate of 90 per cent. The overall egg count reduction of the group

TABLE I. DOSAGE SCHEDULE

PATIENT'S WEIGHT	TOTAL DAILY DOSE OF PIPERAZINE CITRATE SYRUP	TOTAL DAILY DOSE IN TERMS OF PIPERAZINE HEXAHYDRATE
15-30 pounds	5.0 c.c. (2.5 c.c. b.i.d.)	0.5 Gm.
31-60 pounds	10.0 c.c. (5.0 c.c. b.i.d.)	1.0 Gm.
61 pounds and over	20.0 c.c. (10.0 c.c. b.i.d.)	2.0 Gm.

TABLE II. TREATMENT OF ASCARIS LUMBRICOIDES INFECTIONS WITH PIPERAZINE (PIPERAZINE HEXAHYDRATE)

NO.	AGE (YEARS)	WEIGHT (POUNDS)	DAYS OF THERAPY	GRAMS DRUG PER DAY	EGG COUNT PER C.C. FECES		
					BEFORE TREATMENT	AFTER TREATMENT	PER CENT REDUCTION
1	6	48	5	1.0	8,100	0	100
2	8	66	5	2.0	7,700	0	100
3	10	77	5	2.0	8,400	0	100
4	13	114	5	2.0	4,500	0	100
5	13	66	5	2.0	2,200	0	100
6	6	54	5	1.0	16,300	0	100
7	7	47	5	1.0	2,500	0	100
8	13	77	5	2.0	11,800	0	100
9	12	71	4	2.0	9,400	0	100
10	11	116	4	2.0	3,300	0	100
11	11	52	4	1.0	11,200	0	100
12	15	128	4	2.0	600	3,200	0
13	15	160	4	2.0	100	0	100
14	12	90	4	2.0	10,300	0	100
15	9	62	4	2.0	500	0	100
16	12	84	4	2.0	1,300	0	100
17	7	68	4	2.0	2,000	0	100
18	10	68	4	2.0	10,500	9,900	5
19	13	82	4	2.0	200	0	100
20	11	72	4	2.0	48,400	0	100
21	10	74	4	2.0	2,000	0	100
22	8	61	4	2.0	46,700	0	100
23	15	112	4	2.0	44,700	0	100
24	10	68	3	2.0	43,200	0	100
25	12	78	3	2.0	34,900	0	100
26	6	46	3	1.0	15,300	0	100
27	13	83	3	2.0	12,100	0	100
28	8	70	3	2.0	9,500	0	100
29	13	81	3	2.0	5,800	0	100
30	11	71	3	2.0	4,400	0	100
31	6	60	3	1.0	3,400	0	100
32	11	78	3	2.0	3,300	0	100
33	7	46	3	1.0	2,600	0	100
34	8	66	3	2.0	1,500	0	100
35	11	74	3	2.0	500	0	100
36	10	58	3	1.0	8,100	500	100
37	10	84	3	2.0	100	0	100
38	13	100	3	2.0	1,000	0	100
39	6	54	2	1.0	36,100	0	100
40	13	82	2	2.0	16,500	7,500	55
41	9	68	2	2.0	12,600	0	100
42	16	122	2	2.0	10,000	0	100
43	10	65	2	2.0	7,200	0	100
44	9	52	2	1.0	5,200	0	100
45	8	71	2	2.0	3,400	2,900	15
46	6	45	2	1.0	3,400	0	100
47	9	61	2	2.0	3,000	0	100
48	9	61	2	2.0	2,000	0	100
49	11	87	2	2.0	700	0	100
50	6	45	2	1.0	1,000	0	100
51	14	91	2	2.0	300	0	100
Total					499,800	24,000	95.2

was 95.2 per cent (Table II). The egg counts of three patients were reduced, although complete cure was not achieved, and in two instances the egg count was not reduced following treatment. Many of the children reported passing living ascarides during treatment, usually during the first two or three days of therapy. It was impossible to obtain an accurate count of the worms passed. The passage of live worms may be of significance, as it is possible that ascarides killed by an anthelmintic may be digested or decomposed in the intestine, liberating potentially toxic substances which might be absorbed by the host.

Examination of Table II reveals the following cure rates according to the number of days of therapy:

5 days' therapy— 8 of 8 cured, 100%
4 days' therapy—13 of 15 cured, 87%
3 days' therapy—14 of 15 cured, 93%
2 days' therapy—11 of 13 cured, 85%

It is recognized that the individual series are too small to determine the minimum days of therapy required for a 100 per cent cure. No doubt a larger series of patients treated for five days would reveal an occasional failure or partial failuure. Brown and Sterman[6] reported nine out of eleven patients (82 per cent) cured following seven consecutive days' therapy, although as the drug was administered at home by the children's parents there is the possibility that every dose was not taken.

In the egg counts listed in Table II, a count of 1,000 eggs per cubic centimeter of feces represents one worm, approximately. Usually it is the heavily infected patients from whom all the worms are not removed by anthelmintics. However, in the present study the treatment failures or partial failures were in patients harboring an estimated one, three, eight, ten and sixteen worms, whereas patients harboring thirty-four, thirty-six, forty-three, forty-four, forty-six, and forty-eight were completely cured.

It would be expected that treatment failure would be related to the amount of piperazine received by the patient per kilogram of body weight. However, patient 18, whose egg count reduction was only five per cent, received 64 mg. of drug per kilogram of body weight for four days; yet patient 23, with an egg count four times as large, had all of her worms eliminated by 39 mg. per kilogram. Similar examples are present in the data. It is possible that the location of the worms in the host's small intestine, presence of certain foods, or different absorption rates of the drug by the host may be important factors in the therapeutic failures. Four children who were not cured by the first course of therapy were retreated several weeks later and three of them were freed of their Ascaris infection (Table III).

In view of the results it would appear that a two- to five-day course could be given and be repeated two weeks later if eggs were still present in the stool at that time. A five-day course of treatment presumably should give the highest cure rate and would necessitate the fewest number of second courses of therapy. It is possible that larger amounts of piperazine hexahydrate could be employed and that a one- or two-day course of therapy would be sufficient. Fayard[4] gave 7.0 Gm. (as hexahydrate) over a period of two days without untoward effects, but as stool examina-

tions were not routinely done we are unable to estimate the efficacy of this course of treatment.

Clinical experience with piperazine dates back to the 1890's when it was used extensively in gout, urinary lithiasis, and rheumatism on the mistaken theory that it increased the solubility of urates and increased uric acid excretion. Daily doses ranging from 0.5 to 10.0 Gm. were employed. Patients were given 1.0 Gm. daily for thirty to 150 days, 1.0 to 2.0 Gm. daily for sixty days, 3.0 Gm. daily for fifteen days, and 6.0 Gm. daily for six days. Many of the reports on the use of piperazine in man mention the absence of side reactions. Cushny[9] stated that piperazine seems to induce no symptoms in man or animal even when used in large quantities. Hanzlik,[10] however, in an extensive article summarizing the use of piperazine, calls attention to undesirable side reactions such as urticaria, headache, vomiting, diarrhea, tremor, incoordination, and muscular weakness. The side reactions were observed most frequently after the administration of large doses in aged or debilitated patients.

Recently piperazine citrate has been used extensively in the treatment of human enterobiasis (pinworm).[11, 12] When used (as piperazine hexahydrate) in recommended doses of 2.0 to 3.5 Gm. daily for adults for fourteen days, no side reactions have been observed except an occasional urticaria. K. F. Chan and I have treated 150 pinworm-infected patients with ten- to fourteen-day course of piperazine citrate without encountering side reactions. However, White and Standen[13] report side effects in twenty patients who were given piperazine hydrate for pinworm. Giddiness, lack of coordination, difficulty in focusing vision, and a sense of detachment were noted. These effects, for the most part, were mild, and recovery was rapid once therapy was stopped. These workers suggest that the side effects were due to the drug being taken in doses considerably in excess of their recommended 50 to 75 mg. per kilogram. The overdosage, which was as great as 100 per cent, was due presumably to the great variation in the capacity of the domestic tablespoon which was used in measuring the syrup and also to the high meniscus formed by the thick syrup embodying the piperazine, which also would lead to even greater amounts being taken.

Recently Sims[14] reported the following toxic effects in a patient who was treated for pinworm: sense of detachment, flashes on closing the

TABLE III. SECOND TREATMENT OF ASCARIS LUMBRICOIDES INFECTIONS WITH PIPERAZINE (PIPERAZINE HEXAHYDRATE)

(Retreatment of the four *Ascaris lumbricoides*-infected patients not cured by the first course of piperazine hexahydrate)

NO.	AGE (YEARS)	WEIGHT (POUNDS)	DAYS OF THERAPY	GRAMS DRUG PER DAY	EGG COUNT PER C.C. FECES		
					BEFORE TREATMENT	AFTER TREATMENT	PER CENT REDUCTION
12	15	128	4	2.0	3,200	0	100
18	10	68	4	2.0	9,900	0	100
40	13	82	2	2.0	7,500	4,700	63
45	8	71	2	2.0	2,900	0	100

eyes at night, and the dropping of articles. Sims was employing a dosage schedule of 75 mg. (piperazine hexahydrate) per kilogram of body weight. The patient weighed 59 kilograms and, hence, the calculated dose was 4.4 Gm. daily; yet due to the large size of the tablespoon with which she measured the syrup this patient was evidently taking over 6.0 Gm. per day. In the course of a week she took 42 Gm. instead of the intended 28 Gm.

Data on the absorption and excretion of piperazine are not available, as a method of its determination in blood, urine, and feces is not available. Chronic toxicity studies by de Beer[15] failed to reveal a significant effect on the red blood cell or white blood cell counts. Likewise blood counts on several patients who were undergoing piperazine hexahydrate therapy were all normal. The LD_{50} (oral) dose of piperazine citrate for mice is 11 Gm. per kilogram.

The experience with ten to fourteen days' pinworm therapy with piperazine citrate suggests that side effects from a two- to five-day course for ascariasis should be infrequent and that the drug is not only very effective, but also safe.

SUMMARY

Fifty-one children harboring *A. lumbricoides* were given a syrup containing piperazine hexahydrate by mouth for two to five consecutive days. Ninety per cent of the children passed all of their ascarides as a result of the treatment and the overall egg count reduction of the whole group was 95.2 per cent. There was no evidence of side effects from the therapy.

I wish to express my thanks to Dr. R. D. Collins, Health Officer, Letcher County, Kentucky, for his cooperation in this study.

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PURULENT MENINGITIS IN INFANTS AND CHILDREN

A Review of 409 Cases

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TODAY the physician does not feel the trepidation and despair when confronted with the discovery of purulent cerebrospinal fluid in a child with signs and symptoms of meningeal irritation, that was felt by his predecessors of former years. Thanks to the advent of the antimicrobial era he is able to tell the anxious parents at the onset, with some degree of certainty, that their child has an excellent chance of recovery. However, even today, there must remain some reservations in his mind. Many factors play important roles in the intelligent prognostication of this severe illness. The bacterial agent and its degree of virulence are of paramount importance; the age of the patient must always be considered; the length of the illness, prior therapy, associated conditions, and a host of other factors all enter into the evaluation of each specific illness.

It was with these thoughts in mind that the present study was undertaken. Records for the ten-year period from 1944 through 1953 were reviewed with the purpose of determining the age incidence of meningitis, the incidence of the various bacterial agents, the mortality, and the complications resulting.

During this period it was ascertained that 409 patients with purulent meningitis were admitted to Childrens Hospital. The diagnosis in each incidence was made on one or more of the following criteria: discovery of purulent cerebrospinal fluid, isolation of bacteria, or the finding of gross and/or microscopic evidence of meningeal inflammation at autopsy.

CAUSE

Bacteria were isolated from the cerebrospinal fluid in 318 of the 409 cases. In ninety-one cases the cultures were sterile. When this large group is broken down into the various bacterial agents as they occurred during each year of the study, the figures as shown in Fig. 1 are obtained. From this it can be seen that *Hemophilus influenzae* is the most common cause found at this hospital. This is followed by *Neisseria meningitidis, Mycobacterium tuberculosis, Diplococcus pneumoniae,* and *Escherichia coli* in that order. Only a very few cases of salmonella, micrococcus, streptococcus, and pseudomonas were found.

AGE INCIDENCE

When the total group is analyzed the early incidence of meningitis is well demonstrated (Fig. 2). Slightly less than one-half the cases, 47 per cent, occurred during the first year of life. Even more striking is the fact that more than 25 per cent occurred in the first six months of life. Furthermore, more cases were seen in the first month than in any other month.

From the Department of Pathology, Childrens Hospital, Los Angeles, and the School of Medicine, University of Southern California.

CAUSE	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953	TOTAL	% MORT. 10 YR.	% MORT. LAST 5 YR.
H. INFLUENZAE	4/2	4/0	4/2	8/1	13/1	4/0	13/0	9/0	18/1	29/1	106/8	7.5	2.7
UNKNOWN	7/3	2/2	6/5	1/0	8/6	11/5	17/5	10/4	8/2	21/8	91/40	44	36
N. MENINGITIDIS	7/1	5/3	3/0	7/0	4/2	3/1	5/0	5/0	16/2	17/3	72/12	16.6	13
M. TUBERCULOSIS	6/6	3/2	4/4	9/7	6/3	8/6	6/4	4/3	3/3	6/2	55/40	73	66
D. PNEUMONIAE	6/2	3/0	2/0	5/0	6/2	5/0	5/0	1/0	2/1	6/1	41/6	14.6	10.5
E. COLI		3/3		1/0	2/1		5/3	2/2	3/1	3/2	19/12	63	62
SALMONELLA	1/1	1/0						1/1	2/0	1/1	6/3		
MICROCOCCUS			2/1			1/0		1/1	1/0	1/0	6/2		
STREPTOCOCCUS	1/0			1/0			1/0	1/0	1/0		5/0		
PSEUDOMONAS						1/1	1/0	2/1	1/1		5/3		
PARACOLON								1/1	1/1		2/2		
PROTEUS									1/0		1/0		
									TOTAL		409/128	31	26

Fig. 1.—Incidence of the various types of meningitis diagnosed during each year of the study. Number of cases in upper left; number of deaths in lower right.

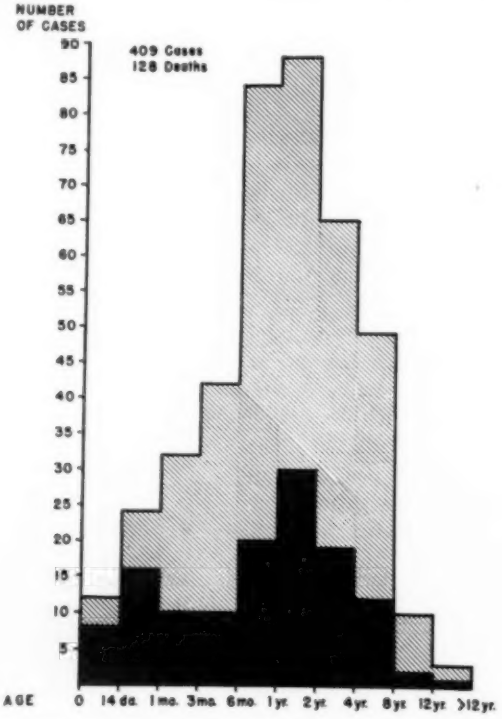

Fig. 2.—Age distribution of 409 cases of meningitis. Fatal cases are in black.

MORTALITY

There were 128 deaths in the entire group, a mortality of 31 per cent (Fig. 1). Exactly 50 per cent of the deaths were in the first year of life, while in the first six months of life 34 per cent of the deaths occurred. The chances of survival increased with age. In the first month of life 24 of the 36 patients expired, whereas during the second year of life 30 of the 88 patients expired. There were 145 cases with 60 deaths in the first five years of this study and 264 cases with 68 deaths in the last five years.

HEMOPHILUS INFLUENZAE MENINGITIS

H. influenzae was isolated in the spinal fluid of 106 patients. In this group there were 90 recoveries without sequelae, eight deaths, and eight poor results.

This form of meningitis is most commonly seen between 6 months and 4 years with one-third of the cases occurring in the second six months of life (Fig. 3). Less than one-half occurred in the first year of life. None occurred prior to 2 months.

The mortality for the ten-year period was 7.5 per cent. In the first five years of the study there were 33 cases with 6 deaths, while in the last five years there were 73 cases with 2 deaths. The second patient who had deaths. The last patient who died responded well to initial therapy, as demonstrated by sterile spinal fluid and temporary clinical improvement, but died of an overwhelming resistant staphylococcal septicemia. At autopsy only minimal inflammation of the meninges was noted. This case will be reported in greater detail in a paper from this hospital concerning the experience with resistant staphylococcal infections.[1]

Eight patients recovered from the meningitis but demonstrated residual signs. This included convulsions, retardation, spasticity, ataxia, partial and complete deafness, hydrocephalus, and a questionable subdural effusion (not proved by subdural tap). There was one recurrence of *H. influenzae* meningitis with admission to another hospital and death at a later date. This boy was known to have a congenital heart lesion.

During recent years much has been written regarding the high incidence of subdural effusions secondary to

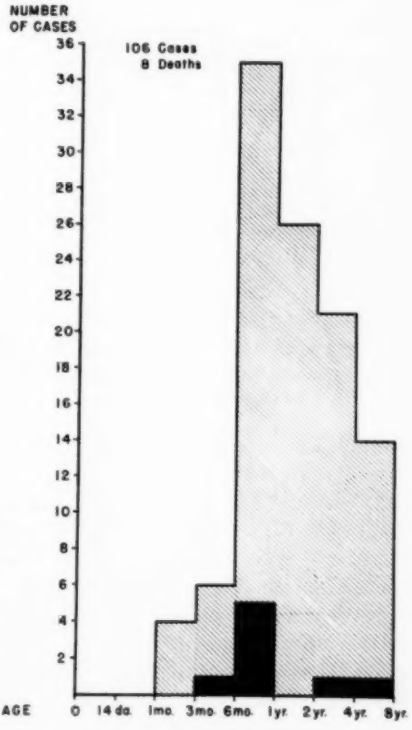

Fig. 3.—Age incidence of *H. influenzae* meningitis. Fatal cases are in black.

meningitis.[2, 3, 4, 5] It has been stressed that this is most common with *H. influenzae* meningitis. Subdural taps have been advocated at the slightest provocation. Since the latter part of 1951 subdural taps have been done on nearly all patients with *H. influenzae* meningitis with open anterior fontanels in whom any symptom which might point toward an effusion was elicited. This group included 18 patients, 9 of whom demonstrated fluid. Prior to 1951 the diagnosis was made on one occasion apparently on clinical grounds alone. All nine of the proved cases recovered without residuals. Only the patient with a questionable diagnosis did poorly. Of these patients only two required surgery. In one a craniotomy was done with surgical evacuation of the membrane, while in the other no membrane was found when burr holes were made. The remaining seven patients had from as little as 3 to 4 c.c. of fluid on one side, found only at one time, to bilateral collections of fluid which became dry after repeated drainage. It should be stressed that the initial tap was dry in several of these patients and only upon subsequent taps at the same site was fluid recovered.

Blood was drawn for culture initially in 73 patients. In 53, *H. influenzae* was grown from the blood.

MENINGOCOCCAL MENINGITIS

Neisseria meningitidis was cultured from the spinal fluid in 72 cases of meningitis. There were 56 recoveries without residuals, 12 deaths, 3 poor results, and 1 in whom no follow-up was obtained.

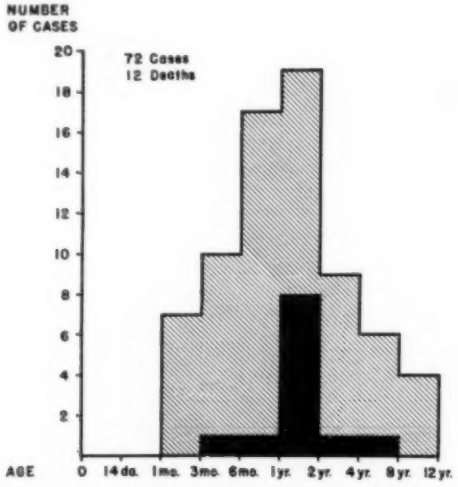

Fig. 4.—Age incidence of meningococcal meningitis. Fatal cases are in black.

The age incidence in this group shows a peak in the second year of life (Fig. 4). Slightly less than half of the cases occurred in the first year. The youngest patient was 1 month old.

The ten-year mortality was 16.6 per cent. There were 26 cases with 6 deaths in the first five years of this study and 46 cases with 6 deaths in the last five years. A review of the 12

deaths is of interest in regard to the acuteness of the illness, and the description of the adrenal glands at autopsy. One child was dead on arrival, 2 died within one hour of admission, 1 at ninety minutes, 2 at four hours, 1 at six hours, 1 at seven hours, 1 at eight hours, 2 at thirty-six hours, and 1 on the fifteenth hospital day. Eleven had the typical purpuric rash and in nine the adrenals were grossly hemorrhagic. The child who lasted fifteen days had chronic leptomeningitis and hydrocephalus with normal-appearing adrenals at autopsy. The initial infection had occurred ten weeks before therapy started, and was thought to be rubeola by the mother. In only 2 were the adrenal glands normal in the face of a clinical course characteristic of the Waterhouse-Friderichsen syndrome.

Sequelae to meningitis occurred in only 3 children. These consisted of retardation and convulsion.

Subdural effusions were found in 5 cases. Three cleared after one to several taps and the recoverey was uneventful. Surgical exploration after draining was required in one. An exudate was seen covering the brain but no membrane was found. This child did well after discharge. One had bilateral effusions requiring a craniotomy with removal of the membrane. He was well upon discharge.

The blood was cultured in 62 of the 72 cases. The cultures were positive in 26 cases. In attempting to correlate the typical skin lesions with bacteriological evidence of meningococcemia, the following data were obtained. In 19 cases cultures were positive in the presence of skin lesions. There were 6 deaths in this group. In 7 cases cultures were positive in the absence of skin lesions; none of these died. In 16 cases skin lesions were present and the cultures were negative; 4 of these expired. In 4 there were skin lesions but the blood was not cultured; 2 of these expired. There were 19 patients without skin lesions and with negative blood cultures; none of these expired.

In addition to these 72 cases there were 6 patients that were signed out as meningococcal meningitis, in spite of repeated sterile blood and spinal fluid cultures. The diagnosis was apparently made on the basis of purulent spinal fluid and the typical rash. These are included in the group of meningitis due to unknown organisms.

TUBERCULOUS MENINGITIS

In the last ten years there were 55 children with tuberculous meningitis admitted to Childrens Hospital. Of these, there were 40 deaths, 7 recoveries with residuals, 4 recoveries without residuals, and 4 in whom no follow-up was obtained. The last 4 were transferred to another hospital during the course of their illness.

All but 6 of the patients developed meningitis between 1 and 8 years of age. Only 5 were under one year of age and none of these were under 6 months (Fig. 5).

The ten-year mortality is 73 per cent. There were 28 cases in the first five years of this study with 22 deaths and 27 cases in the last five years with 18 deaths.

Seven children developed complications following the initial illness. These included hydrocephalus, convulsions, blindness, and chronic meningitis. Deafness was the only residual in one boy and was thought to be secondary to therapy.

The majority of this group has been reviewed by Perry[6] and needs no further comment.

PNEUMOCOCCAL MENINGITIS

There were 41 patients with pneumococcal meningitis admitted during the ten-year period of this study. Of these there were 22 recoveries without residuals, 13 recoveries with residuals, and 6 deaths.

The age incidence for this group reveals a very wide spread with one case diagnosed at 3 weeks of age and one at 14 years (Fig. 6). Over one-half of the patients were under 1 year of age.

The ten-year mortality is 14.6 per cent. There were 22 cases with 4 deaths in the first five years of this study and 19 cases with 2 deaths in the last five years.

The incidence of complications in this group is higher than in any of the major groups in this study. Sequelae

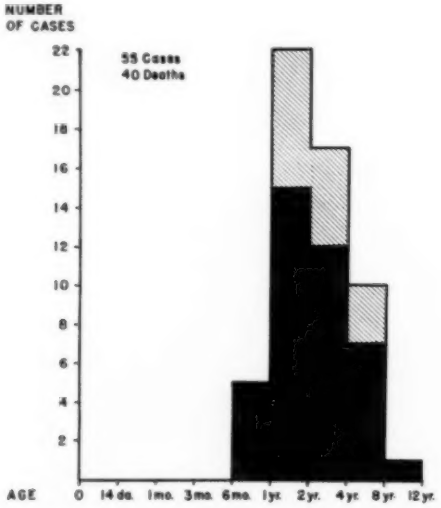

Fig. 5.—Age incidence of tuberculous meningitis. Fatal cases are in black.

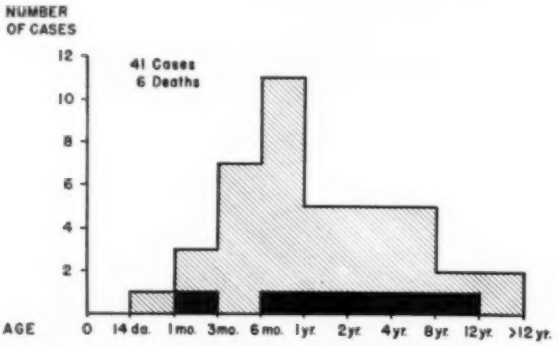

Fig. 6.—Age incidence of pneumococcal meningitis. Fatal cases are in black.

consisted of deafness, hydrocephalus, quadriplegia, aphasia, behavior problems, and evidence of precocious puberty. There was an inadequate follow-up in two and one was hospitalized in another hospital because of recurrence of meningitis. Slight right arm and leg spasticity was noted in one infant who developed an infected left subdural effusion that cleared without surgery.

One infant had bilateral subdural effusions which required a craniotomy for evacuation of the membranes. Upon discharge she appeared normal.

Primary foci were demonstrated in several of the children. Eight had mastoiditis, several of whom required surgery. Four children had acute to chronic purulent otitis media. Three had bronchopneumonia. Two developed meningitis secondary to fracture of the cribriform plate with cerebrospinal rhinorrhea. One had laryngitis. One had recurrent fibromas of the nose requiring frequent surgery. One child died because he fell upon a lead pencil forcing it through his eye into the base of the brain with a subsequent meningitis and septicemia. One was a case of sickle cell anemia with many admissions for bronchopneumonia.

ESCH. COLI MENINGITIS

Nineteen cases of *Esch. coli* meningitis were admitted during this ten-year period. There were 12 deaths, 4 recoveries without residuals and 3 recoveries with residuals. This group includes 2 patients with anomalies of the spinal cord, 1 of whom expired subsequent to a ventriculoperitoneal shunt.

An analysis of the age incidence for this group is striking. All 19 patients were under 1 year of age, while 13 occurred prior to 1 month of age (Fig. 7).

The mortality for this type of meningitis is high; almost two-thirds of the patients died. During the first five years of this study there were 6 cases with 4 deaths, while there were 13 cases with 8 deaths in the last five years.

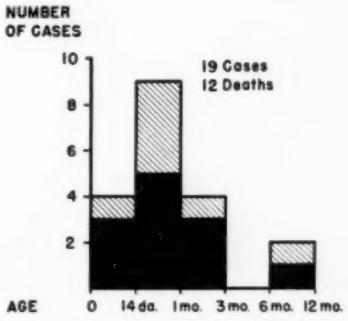

Fig. 7.—Age incidence of *Esch. coli* meningitis. Fatal cases are in black.

Of those patients who recovered but suffered sequelae, one had a meningocele. One was a premature infant who was ill from birth. At two months, when meningitis was discovered, pus was found on a subdural tap. He developed hydrocephalus and required placement. One developed meningitis secondary to an infected subdural hematoma thought to be a result of birth trauma. Hydrocephalus followed and blindness was suspected.

Three children had subdural hematomas; one of these died, while the other two developed hydrocephalus. Because of the early age of all three of these patients it is probable that the hematomas occurred first as a result of birth trauma, with secondary infection and subsequent meningitis.

SALMONELLA MENINGITIS

There were 6 cases of salmonella meningitis diagnosed in the ten-year period. In this group there were 3 deaths, 2 complete recoveries, and 1 recovery with residuals consisting of retardation and poor vision. *S. bredeney* was isolated in 2, while *S. typhimurium, paratyphosa B, loma linda,* and *panama* were isolated in the remaining 4.

One was a 13-month-old girl, while the remaining were under 3 months of age.

This group has been reported in greater detail in another article.[7]

STAPHYLOCOCCAL MENINGITIS

Micrococcus was isolated from the spinal fluid of 6 patients. There were 2 deaths, and 1 complete recovery. Of the remaining 3, 1 child developed meningitis secondary to a subdural hematoma as the result of trauma. There was also retinal hemorrhage. At the present time he has residual visual and motor defects. One child developed chronic epidural abscesses with subsequent hydrocephalus. One developed meningitis following operation for an old subdural hematoma. At the present he is comatose and draining pus and bone fragments from a chronic scalp and cranial infection.

The oldest patient was 9 years of age and was the only one to recover completely.

STREPTOCOCCAL MENINGITIS

Streptococcus was the agent in 5 cases of meningitis. Three patients recovered completely and 2 recovered with residuals consisting of retardation and spasticity.

The age range was from 3 months to 6 years. One was a case of sicklemia. Alpha streptococcus was found in 2, beta in 1, gamma in 1, and enterococcus in the 3-month-old infant.

PSEUDOMONAS MENINGITIS

Pseudomonas was isolated in the spinal fluid in 5 patients. Three died, and 1 recovered completely. One was born with a meningomyelocele which led to hydrocephalus. At 1 year of age he developed meningitis from which he recovered. The remaining patients were under 6 months of age.

PARACOLON MENINGITIS

Paracolon was isolated in the spinal fluid of 2 infants both of whom expired. One was a 14-day-old boy who had a paracolon sepsis and meningitis. At autopsy a transposition of the great vessels and a vascular ring were also found. The other died at 1 month of age of sepsis and meningitis.

PROTEUS MENINGITIS

Proteus was found in 1 infant; a 1-month-old boy who developed marked hydrocephalus following the infection.

MENINGITIS DUE TO UNKNOWN ORGANISMS

Ninety-one patients with meningitis in whom no organism was isolated were admitted during the ten-year period. In this group there were 43 recoveries without complications, 40 deaths, and 8 recoveries with sequelae. There were 13 patients with various types of neurological anomalies which consisted mainly of defects in the spinal canal.

The age distribution for this group shows a wide and irregular spread (Fig. 8). This is to be expected since the group contains a variety of bac-

terial agents which we were not fortunate enough to isolate. Still more than one-half of the cases occurred in the first year and two-thirds of the deaths were in this same period.

The ten-year mortality for this group was 44 per cent. There were 24 cases with 16 deaths in the first five years of this study and 67 cases with 24 deaths in the last five years. The high mortality is probably due to the many young infants and the number of neurological anomalies contained in this group.

Of the group of 8 patients in whom poor results were obtained, 3 had meningomyeloceles. The remaining dismastoid infections concomitant with or preceding the meningitis, thus placing them in a group similar to pneumococcal meningitis. There were at least 6 children with clinical meningococcal meningitis. Those infants in the neonatal period and those associated with spinal canal anomalies were probably infected with one of the various enteric organisms. There were several who died from other causes and only at autopsy was evidence of chronic or acute meningeal inflammation found. One infant had bilateral tentorial tears. Six children had various types of congenital heart lesions, 2 of whom had brain abscesses. Several had evi-

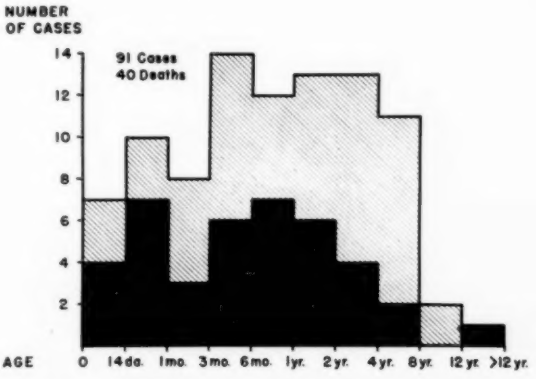

Fig. 8.—Age incidence of meningitis due to unknown organisms. Fatal cases are in black.

played hydrocephalus, convulsions, and hemiparesis. One developed meningitis following surgical evacuation of a recurrent brain tumor.

There were 3 patients with subdural effusions in this group. None required surgery and all recovered without residuals.

This group is of special interest in many respects. Many of the patients pursued a course typical to *H. influenzae* meningitis. Several of the children had pneumonia and/or ear and dence of generalized sepsis with positive blood cultures but without spinal fluid cultures. One died of sepsis resulting from fibrocystic disease of the pancreas. One had galactosemia. One died of chronic glomerulonephritis.

A possible explanation for the increase in the number of sterile cultures in the last five years is the more widespread use of the newer antibiotic agents. At the present time it is a rare patient who enters the hospital with any illness who has not received

a course of antimicrobial therapy before admission was advised. Only those children infected with extremely virulent organisms causing almost immediate prostration reach the hospital in a virginal state. These are the patients who are most likely to die. Those patients who are infected with weaker strains of organisms show less symptoms and are consequently treated at home for a few days before meningeal signs become manifest. On admission though the spinal fluid may contain many cells it has already become sterile. The group that had all the physical signs of meningococcemia with cloudy but sterile spinal fluid is a good example. The fact that all six recovered without sequelae indicates that the organism was of a weaker strain and responded quickly to only moderate amounts of antibiotics.

COMMENT

When confronted with a child who has the signs and symptoms of purulent meningitis, the most likely bacterial agent is *H. influenzae*. However, *N. meningitidis, M. tuberculosis, D. pneumoniae* and *Esch. coli* are cultured with enough frequency to be considered in each differential diagnosis. Though there were only 19 cases of *Esch. coli* meningitis, it must be remembered that of the 19 cases in the first month of life in which organisms were isolated 13 were due to *Esch. coli*. In fact, aside from one case of pneumococcal meningitis, the entire group was caused by enteric organisms.

The mortality of 7.5 per cent for *H. influenzae* meningitis compares well with the death rate of the recently reported series of patients treated with chloramphenicol.[8-13] Of a total of 93 cases collected from the literature there were six deaths, a mortality of 6.5 per cent. During the last five years of our study the mortality was only 2.7 per cent. At this hospital chloramphenicol is used infrequently and each patient with meningitis receives several antimicrobial agents. A forthcoming article will discuss in greater detail the mode of therapy and clinical course during the various eras of therapy in this form of meningitis.

The mortality in meningococcal meningitis is slightly higher than in the series reported by Lepper and associates.[14] In this group there were 130 patients with 11 deaths, 10 of whom were patients with fulminating meningococcemia. We had 12 deaths in 72 cases, 11 of which were fulminating meningococcemias.

The 14.6 per cent mortality for pneumococcal meningitis is much better than the 31 per cent mortality in a group of 84 patients treated with massive doses of parenteral penicillin collected from the literature.[15, 16, 17] Only the series of 31 cases with three deaths reported by Gibson and James[18] shows better results. This group was treated with several agents, rather than penicillin alone. The incidence of residuals in our group is higher than that found in a comparable group reported by Daisley.[19] He reviewed 56 cases in which there were 12 survivals with residuals. However, his mortality was 41 per cent.

Subdural effusions secondary to meningitis have not been a frequent or serious occurrence at this hospital. Fluid was found in the subdural spaces of only 19 patients. Craniotomy was done in 4 cases and a membrane was found in 3. All 4 of these recovered completely. Burr holes

were made in one but no membrane was seen. He is well. Of the remaining 14 cases only one demonstrated a slight residual spasticity of one side. This does not include the 5 patients with subdural hematomas as the result of trauma and subsequent meningitis. From these findings we are not in agreement with those who advocate craniotomy in every case of subdural effusion.[20]

One cannot help wondering whether the etiology of some of these effusions might not have an iatrogenic factor. In several instances it was not until the second attempt at tapping the subdural space that fluid was found, and then only in small amounts. It does not seem improbable that the delicate arachnoid membrane could be injured with a needle point to the extent of allowing the escape of spinal fluid or serum into the subdural space which would be discovered when the area is re-explored.

The incidence of complications secondary to meningitis is fairly high in this series. Of the 281 survivors there were 50 (18 per cent) who suffered sequelae. A comparable group of cases for comparison could not be found in the literature.

CONCLUSIONS

In this hospital:

1. *H. influenzae* is the most common cause of meningitis in children.

2. *Esch. coli* is the most common cause in the neonatal period.

3. More cases of meningitis occur in the first month of life than in any other month.

4. Almost one-half of the cases occur in the first year of life.

5. The mortality in meningitis decreases sharply after the first month of life.

6. Prognosis is most favorable in *H. influenzae* meningitis and least favorable in tuberculous and *Esch. coli* meningitis.

7. A high incidence of complications is associated with pneumococcal meningitis.

8. Subdural effusion secondary to meningitis is not a common or serious complication.

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PNEUMOTHORAX AND PNEUMOMEDIASTINUM IN THE NEWBORN INFANT

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DYSPNEA and cyanosis are always distressing signs, particularly in the neonatal period. In the differential diagnosis very little consideration is given in most textbooks to pneumothorax and/or pneumomediastinum as etiological factors. Although the latter conditions have been considered rare, they are being reported more frequently,[1, 2, 3] and are probably overlooked in some cases.

We have prepared a classification of the causes of pneumothorax and pneumomediastinum in infancy as follows:

1. Diseases of the lung (e.g., pneumonia with abscess formation)
2. Congenital defects (e.g., bronchopleural fistula, cysts, and pulmonary vessel anomalies)
3. Traumatic injuries (direct fracture of the ribs or clavicle, perforating wounds of the larynx, trachea, or bronchus, wounds of the neck or diaphragm)
4. Mechanical obstruction
   1. External (enlarged thymus or thyroid, cord around neck)
   2. Internal (mucus or vernix in the air passages)
5. Idiopathic or unknown

The following two cases are illustrative of different mechanisms involved in the production of this condition.

CASE REPORTS

CASE 1.*—S. B., a 7 pound 1 ounce white female infant, was delivered with low forceps after an easy four-hour labor. The mother's prenatal course had been uneventful. Nitrous oxide analgesia was used for delivery and the infant was slow in breathing. Laryngoscopy was performed shortly after delivery and thick mucus was aspirated. Continuous oxygen was administered but during the first twenty-four hours the infant was said to have had "glottic spasm" and had three convulsions. The latter were controlled by sodium phenobarbital hypodermically. On the second day the infant apparently aspirated some formula and was again laryngoscoped. Examination at this time revealed the heart shifted to the right, the left side of the chest hyperresonant, and the breath sounds diminished. Roentgen examination (Fig. 1, *A* and *B*) revealed left pneumothorax and pneumomediastinum. Approximately 25 c.c. of air was aspirated from the left pleural cavity with marked improvement in color, and the breath sounds became more audible. Sedatives and clyses were administered. The following day (third post partum) 25 c.c. of air was again aspirated. Because of the dusky color and severe dyspnea the infant was transferred to the Childrens Hospital, San Francisco. Physical examination on admission showed a markedly dyspneic and cyanotic infant, breathing around 60 per minute. The infant was extremely lethargic, and the pulse rapid and thready. There was a cephalic cry, and the Moro reflex was not elicited. The sternum seemed protuberant, and the heart was displaced to the right. The left chest was hyperresonant and there were no breath sounds audible. The blood showed hemoglobin 21 Gm., red blood count 4.9 million, white blood count 15,100, polymorphonuclears 77 per

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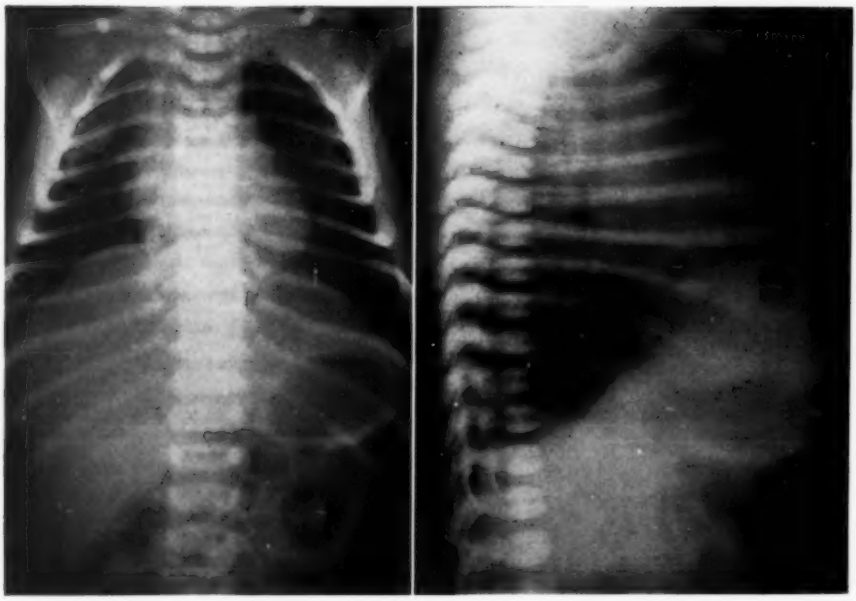
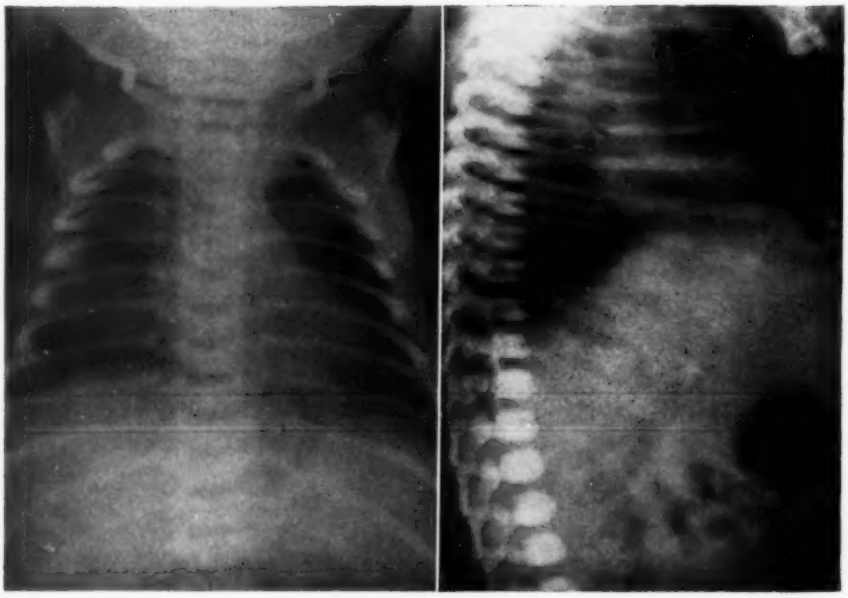
*Our sincere thanks are due to Drs. C. R. Leininger, Jr., and T. L. Grayson for their kind cooperation in supplying a great deal of the data about this patient.



A. *B.*



C. *D.*

Fig. 1.—*A* and *B*. The trachea is displaced to the right. The left lung is compressed by air. There is a small amount of air in the right pleural cavity and the right upper lobe is compressed. The lateral view shows a pneumomediastinum. *C* and *D*. Six days later. There is no evidence of pneumothorax. No shift of the mediastinum is seen in the anterior view. In the lateral view, however, there is still a small amount of air in the anterior mediastinum.

cent, lymphocytes 15 per cent, monocytes 2 per cent, eosinophils 1 per cent. The urine contained a trace of albumin. The humidifier and oxygen tent were used continuously and by evening of the admission day the respirations had slowed to 35 per minute and breath sounds were audible over the left chest. Clyses of 5 per cent glucose in water and normal saline solution were administered during the following two days. Penicillin 150,000 units daily was given parenterally for the next nine days. Sterile water was offered orally on the fifth day of life and, since it was retained, a Dryco formula was started the next day. The following day an evaporated milk mixture was given with excellent results. On the seventh day oxygen was discontinued. Repeat x-ray examination showed a slight pneumomediastinum but no pneumothorax (Fig. 1, *C* and *D*). The breath sounds were quite normal. The temperature, which on admission was 36.4° C., returned to normal after two days and remained so until discharge on the thirteenth day of life. The weight at discharge was 7 pounds 11 ounces, the same as at birth. At 1 year of age the infant was entirely normal, both mentally and physically.

This patient apparently suffered from a mechanical obstruction due to mucus in the air passage. Repeated aspirations, continuous oxygen administration with humidification, and careful attention to fluid and electrolyte balance effected a complete cure.

CASE 2.—W. G. The mother, a 27-year-old para ii, had had "hormones" the first three months of pregnancy. Because of premature rupture of the membranes the infant was delivered with low forceps almost one month before the expected date. Under caudal anesthesia a 5 pound 11 ounce male was easily delivered and cried spontaneously. The color was quite good but the infant was routinely placed in an incubator and oxygen (5 L. per minute) was administered in the premature nursery. Five milligrams Hykinone was injected shortly after delivery. At twenty-four hours, a low-fat formula was started, 15 to 30 c.c. every three hours. On the second day the infant seemed dusky when taken out of oxygen and was spitting up some mucus. By the third day the respirations became rapid and labored and the duskiness progressed to cyanosis. Examination revealed the heart was shifted to the right, there was hyperresonance over the left chest, and the breath sounds were greatly diminished. Atelectasis of the left lung was suspected. Continuous O_2 (5 L. per minute) was administered and 150,000 units of penicillin was given intramuscularly. X-ray examination (Fig. 2, *A* and *B*) showed a left pneumothorax and pneumomediastinum. On the fourth day the color of the infant seemed better and the shift of the mediastinal structures less marked. The breath sounds were more audible. Chest retraction, noted since the second day, was now gone and the mucus expectoration had stopped. On the fifth day O_2 was discontinued. Repeat roentgen examination (Fig. 2, *C* and *D*) showed a normal chest. The infant was discharged on the seventh day, weighing 5 pounds 1¼ ounces and taking 40 to 50 c.c. of Olac formula eagerly. When seen at 9 months of age the infant was 27¼ inches long and weighed 20 pounds 10 ounces. He was sitting up well and beginning to pull himself up in the play pen.

We believe this patient illustrates the idiopathic type of pneumothorax and pneumomediastinum. Oxygen and antibiotic were utilized as in the previous case. However, aspiration was not deemed necessary. This patient also made a complete recovery.

COMMENT

The pleura of the infant being richer in cellular tissue and having less connective and elastic tissue than the adult is thus easier to tear. Air may pass directly through a tear in

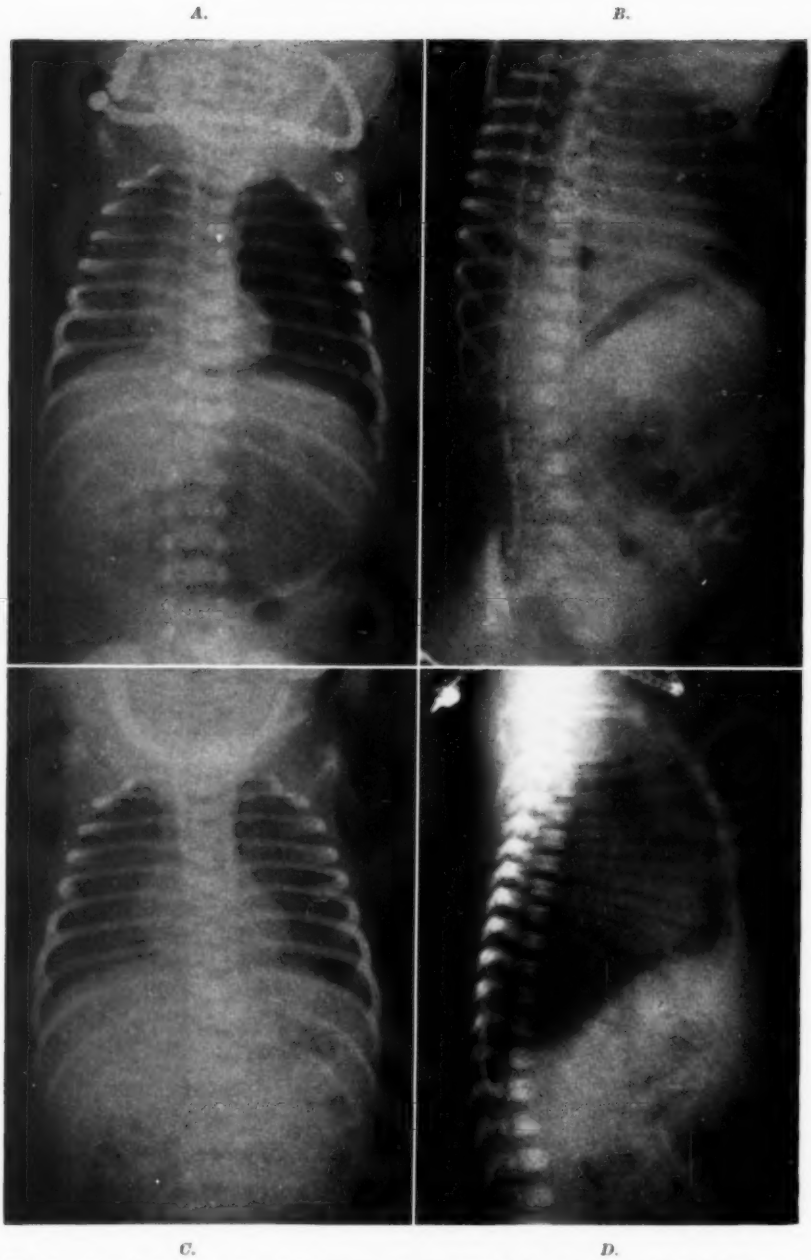


Fig. 2.—*A* and *B*. There is a left pneumothorax completely encircling the left lung on all aspects, including the diaphragmatic, and with the left lung compressed to approximately two-thirds of its original volume. There is also some air in the anterior mediastinum. The mediastinal structures are shifted to the right and the right lung is incompletely aerated, probably due, at least in part, to pressure from the shift in the mediastinum, though there may also be an element of patchy atelectasis. The left lung is also incompletely aerated, which again is probably due to the compression from the pneumothorax. *C* and *D*. Four days later. The lung fields are now fully expanded. The mediastinum is now in the midline. There is no evidence of any residual pneumothorax or pneumomediastinum.

the visceral pleura and reach the pleural space or may pass along the vascular sheaths to the mediastinum and from there rupture through the parietal pleura into the pleural cavity. Air may travel to the interstitial tissue of the opposite lung, the neck, or along the perivascular sheaths through the diaphragm into the retroperitoneal space. It may penetrate into the peritoneal cavity and give rise to pneumoperitoneum, and may even extend into the groins.

The occurrence of pneumomediastinum and pneumothorax in infancy, as reported in the literature, is rather infrequent. Keefe and Jones[4] in more than 4,000 newborn infants stated that routine anteroposterior and lateral x-rays of the chest failed to reveal any case of pneumomediastinum. Davis and Stephens[5] found six cases of pneumothorax in a series of 720 examinations of newborn infants with respiratory distress. In 1935 Glaser and Landau[6] collected seventeen cases of pneumothorax in the newborn infant, with the left side involved most frequently. De Costa,[7] a few years later, could find only sixty-seven cases of pneumothorax recorded in infancy, forty-six of which occurred in the first ten days of life. The latter author stated that pneumothorax occurs more frequently in males and predominates on the right side. Bilateral pneumothorax was found in seven cases in this series.

Some cases of pneumothorax and pneumomediastinum probably produce few if any symptoms. Usually there is an insidious onset with respiratory and/or cardiac distress. Cyanosis, dyspnea, cough, difficulty in nursing, and fever have been recorded. The chest may appear larger on the affected side, and the apex of the heart may be displaced to the opposite side. Resonance is increased on percussion, while the breath and heart sounds are usually diminished or absent.

Roentgen examination is essential for a definite diagnosis of pneumomediastinum. It is important to obtain films in the anteroposterior and lateral projections. In the differential diagnosis roentgenologically, atelectasis with compensatory emphysema of the contralateral lung, giant congenital lung cyst, and diaphragmatic hernia must be considered. The lateral projection film usually proves decisive in establishing the diagnosis.

The prognosis is said to be worse the earlier in life the pneumothorax and/or pneumomediastinum develops. It is dependent also upon the associated lung condition (infection, congenital anomaly, etc.). DeCosta[7] reported 42 per cent mortality, the majority with symptoms developing in the first twenty-four hours. Disappearance of the air may take place in from two to sixty days. Recovery seems to be complete in the surviving idiopathic cases. Both of our patients made a complete recovery.

Prophylaxis consists in the avoidance of any traumatic procedure in instituting respiration. Careful aspiration to avoid obstruction should be the initial step. With dyspnea and cyanosis, oxygen is indicated and stimulants may be helpful. Increase in the severity of symptoms necessitates aspiration of air. Usually a single aspiration suffices but it may be necessary to institute continuous drainage. Increasing the pneumothorax has been suggested to produce compression of the alveolar rupture

and seal off perivascular spaces so that further leakage is prevented. This procedure is not without danger and we would not recommend it. Chemotherapy and antibiotics to prevent infection should be utilized.

SUMMARY

Two cases of pneumothorax and pneumomediastinum in the newborn infant are reported. Both patients recovered, one with conservative therapy, the other with repeated aspirations. There have been no recurrences and no sequelae.

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A NOTE ON A SCREENING TEST OF ARTICULATION OF SPEECH SOUNDS

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MOST pediatricians are currently interested in the behavior as well as the physical growth of children. Because of this a screening test of speech sound articulation should be a useful instrument for pediatricians.

This article briefly reports the development and standardization of such a screening test for use with children 3 years of age and older. As a screening test, it is used to separate those children who are making normal progress in the articulation of speech sounds from those who may need special attention in this area of development.

The screening test consists of 50 sounds tested in 40 words. The child repeats the words after the examiner or in response to stimulus pictures, whichever technique is best adapted to the particular child. The accuracy or inaccuracy of production of each of the critical sounds printed in bold face type in Table I is checked with no attempt to describe the inaccuracy. The score on the test is the number of correctly produced sounds.

Any child receiving a score below the cut-off score for his age level as given in Table II can be considered retarded in articulation of speech sounds and should be referred to a speech therapist for further study. For children over 8, the scores at 8 years should be used, since by this age most children have developed adult level of accuracy in the articulation of speech sounds.

The 50 speech sound items included in the screening test of articulation were selected through an item analysis of 113 speech sound items. They are the items which discriminated most satisfactorily between good and poor articulation in nursery school and kindergarten children at the University of Minnesota, Institute of Child Welfare. The children receiving the highest 27 per cent of the scores made up the group with good articulation, and those receiving the lowest 27 per cent made up the group with poor articulation.[1]

The screening test is both reliable and valid. When the sounds included in the test were measured both in words and sentences, the test re-test correlations for single age groups from 2 to 5 ranged between .93 and .99 on comparatively small samples. The correlations between external criterion and both screening and more complete articulation tests are similar. For the 2-to-5 age groups the correlation with chronological age and the 113 item test is .64 and with the fifty-item test .64; the correlation with mental age is .70 and .71.[1] With a sample of 480 children, sixty at each of eight different age levels be-

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tween 3 and 8 years, the correlations between accuracy of initial consonants, medial consonants, final consonants, total number of words, and number of different words used in a conversational situation are similar for a 176-item articulation test and the 50-item screening test.[2] For this same sample the correlations for each age level between the longer test and the screening test range from .94 to .93.

TABLE I. SCREENING TEST WORD LIST FOR CHECKING SPEECH SOUNDS*

1. reach**ing**	21. **thr**ow
2. **sk**ate	22. **pr**esent
3. **br**o**th**er	23. **shr**ink
4. **sh**oe	24. **sw**ing
5. **spl**a**sh**ing	25. **dr**um
6. **sn**ow	26. **st**ove
7. **y**ellow	27. **gl**ass
8. **ch**erry	28. **scr**a**tch**
9. **sl**ed	29. **fr**e**sh**
10. any**th**ing	30. **sm**oo**th**
11. **gr**ass	31. **cr**acker
12. **cl**o**th**	32. **z**ipper
13. **th**ere	33. **pl**ea**s**ure
14. **fl**ower	34. **l**ar**g**er
15. **spr**ing	35. on**i**on
16. **th**umb	36. b**ir**d
17. **tr**uck	37. **str**aw
18. **v**alentine	38. m**u**sic
19. **sp**oon	39. **tw**ins
20. **j**ump	40. **qu**een

*Critical test sounds in bold face type.

The cut-off scores were determined after testing samples of sixty children, thirty boys and thirty girls, selected to form a representative sample according to father's occupation at each half-year level from 3 through 5 and at each year level from 5 through 8. The age intervals were discreet with a variation of only one month from the designated age, i.e., children designated as 4 years ranged in age from 3 years 11 months to 4 years 1 month. The cutting score was determined empirically and somewhat arbitrarily at each age level, after taking account of the form of the distributions, the means and standard deviations, the medians and quartile deviations, and the approximate level of articulation to be expected at each age level. The variation in percentages of children selected for further study reflects the attempt to recognize progress toward accuracy of articulation with increasing age. At 8 years of age, when essentially mature articulation has been achieved by most children, about 8 per cent of the subjects can be expected to receive scores below the cutting score. This percentage closely approximates that reported for articulatory defectives by the White House Conference Committee.[3]

TABLE II. CUT-OFF SCORE ON SCREENING TEST FOR AGES THROUGH 8 YEARS

C.A.	CUT-OFF SCORE	SUBJECTS AT OR BELOW CUT-OFF SCORE	
		NUMBER	PER CENT
3	12	17	28
3½	18	16	27
4	23	9	15
4½	26	12	20
5	31	14	23
6	34	11	18
7	39	7	12
8	44	5	8

Ideally screening and diagnostic tests should agree in classifying articulation as adequate or inadequate. When there is disagreement between the two measures, either some subjects selected as speech defectives according to the diagnostic test are not identified by the screening test or subjects selected by the screening test are classified as having satisfactory articulation by the diagnostic test. Practically the ideal of complete agreement between the screening measure and a diagnostic meas-

ure is never attained. The cut-off scores as determined select for further study more youngsters than may have defective speech in order that fewer children with poor articulation be overlooked. In the normative sample of 480 cases, however, use of the cutting scores would have resulted in only twelve disagreements in classification between the screening and diagnostic tests.

CONCLUSION

A screening test of articulation which may be given at the time of a physical examination to increase understanding of the developmental level of articulation of speech sounds by children is presented with norms for children from 3 through 8. For children 9 years of age and older, the 8-year-old norms apply. A complete report of the construction and standardization of the test has been published previously.[1, 2]

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TRAUMATIC CHYLOTHORAX

Report of Two Cases and Review of Pediatric Literature

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TRAUMATIC chylothorax has been given scant attention in the pediatric literature because of its relatively infrequent occurrence. However, the increased requirement for intrathoracic surgery, especially for the correction of congenital heart disease, may increase the incidence. We wish to present two cases of traumatic chylothorax which resulted from inadvertent injury to the thoracic duct during the course of congenital heart surgery. One case is of special significance because it was cured by a subsequent surgical procedure.

We have collected and summarized all previously reported cases of chylothorax in infancy and childhood in order to elucidate the natural history of the disease. The grave outlook which has been associated with this condition because of its wasting effect on the patient may be made more hopeful by the recent surgical advances and more effective control of the nutritional problem.

CASE REPORTS

Case 1.—B. P., 6-year, 11-month-old white female, was admitted to the hospital with a history of a heart murmur since birth, poor growth, and frequent respiratory infections. Physical examination revealed a frail child, in the twenty percentile for weight and the eight percentile for height. The heart was slightly enlarged; a loud machinery-like murmur, accompanied by a thrill, was audible over the precordium. The blood pressure was 120/0 in the arms. There were no signs or symptoms suggesting subacute bacterial endocarditis or congestive heart failure. Roentgenographic studies revealed a prominent right outflow tract and pulmonary artery. Laboratory tests on admission were normal.

Thoracotomy was performed on the second hospital day and a ductus arteriosus (approximately 7 mm. in diameter and 8 mm. in length) was ligated and divided with the use of a Potts divisional clamp. At no time during the procedure was there any evidence of injury to the thoracic duct or its radicles.

On the first postoperative day the patient developed a croupy cough. On the following day, 150 c.c. of yellowish fluid was aspirated from the chest through the thoracotomy tube. The fluid contained many lymphocytes and small fat globules. In repeated thoracenteses for respiratory distress during the next ten days, a total of 2,700 c.c. of chyle was removed. This contained 125 meq. per liter of sodium, 8 meq. per liter of potassium, 2.8 Gm. per cent total protein, and 3.1 Gm. per cent fat. The patient's clinical condition regressed because of loss of chyle, anorexia, dehydration, salt depletion, and prerenal azotemia.

On the eleventh postoperative day the patient was explored through the previous wound. A large lymphatic

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duct along the posterior wall of the esophagus and a smaller anomalous channel lateral to the esophagus were identified. The chyle came from the left lateral anomalous duct. Both ducts were mobilized and doubly ligated. No further leakage occurred and the chest was closed.

There was no recurrence of the chylothorax. After the second procedure the patient developed symptoms of heart failure, a quiet distended abdomen and widening of the pulse pressure; potassium therapy markedly relieved these symptoms. Three days after the second operation the thoracotomy tube was removed. Roentgenograms on the day before discharge from the hospital revealed nearly complete disappearance of the pleural effusion.

The patient has shown gratifying growth and development, with no recurrence of the chylothorax in the fifteen months since surgery.

CASE 2.—C. E., a fragile 2½-year-old white male child, was admitted to the hospital with a history of cyanosis since birth with no signs or symptoms of congestive heart failure or subacute bacterial endocarditis.

Physical examination revealed a deeply cyanotic child in the ten percentile for height and three percentile for weight. His heart was enlarged to the left anterior axillary line. A loud, widely transmitted systolic murmur, accompanied by a thrill, was heard in the fourth left interspace. His liver was palpable 1 cm. below the costal margin. The remainder of the physical examination was negative.

Laboratory work revealed a packed cell volume of 69 per cent, hemoglobin of 25.2 Gm., and a red blood cell count of 9.10 million. The white blood cell count and differential, and urinalysis were normal.

Roentgenograms of the chest and intravenous angiocardiograms revealed a large pulmonary artery, some increase in vascularity of lungs, evidence of overriding of aorta, and right ventricular hypertrophy. Although Eisenmenger's complex was the probable diagnosis, an exploratory thoracotomy was felt to be warranted. Exploration through the second right intercostal space revealed a large pulmonary artery (pressure 37 cm. water) with a thrill originating from the base. During the procedure there was no suspicion of injury to the thoracic duct system. Respiratory distress accompanied by fever was noted about thirty hours after the operation, with dullness and diminished breath sounds over the right lung base. On the fourth postoperative day, a right pleural effusion was confirmed by roentgenogram. A thoracentesis yielded 80 c.c. of pinkish, odorless fluid which proved to be sterile and contained 2.3 Gm. per cent fat. Six thoracenteses were required during the next sixteen days, each yielding about 130 c.c. of chyle. The patient's course was characterized by listlessness and an irregular fever, which gradually subsided. During the thoracenteses he lost about 1 kilogram in weight but seemed to be eating well. He was discharged under the close supervision of his local physician, who performed several thoracenteses. A chest roentgenogram taken twelve days after discharge home revealed no evidence of pleural fluid. Steady improvement was noted, although several months elapsed before he regained his admission weight.

This patient has been followed for five years without recurrence of the chylous effusion.

REVIEW OF PEDIATRIC LITERATURE

Incidence.—A survey of the literature reveals thirty-four cases of traumatic or "spontaneous" chylothorax in the pediatric age group (0 to 14 years), thirty-two of which are summarized in Tables I and II. Table III lists those cases in which there is doubt as to a traumatic etiology. Two cases were not available for study.

TABLE I. REPORTED CASES OF TRAUMATIC CHYLOTHORAX IN PEDIATRIC AGE GROUP

REF.	AGE AT ONSET	SEX	INCITING CAUSE*	LATENT PERIOD†	SITE	DURATION	OUTCOME	REMARKS
a	4 da.	M	"Spontaneous"	—	Right	1 da.	Died	Normal delivery
b	4 da.	M	"Spontaneous"	—	Left	21 da.	Recovery	Normal delivery
10	4 da.	M	Forceps delivery, asphyxiated at birth	4 da.	Right	10 da.	Recovery	
9	4 da.	?M	"Spontaneous"	—	Right	20 da.	Died	Normal delivery
c	14 da.	M	"Spontaneous"	—	Right	13 da.	Recovery	No known birth trauma or other cause
d	15 da.	M	Cord around neck; vigorous resuscitation	15 da.	Right	21 da.	Died	Ascites at post mortem
e	21 da.	M	"Spontaneous"	—	Right	6 da.	Recovery	Normal delivery; transient cyanosis on first day
f	3 wk.	F	"Spontaneous"	—	Bilateral	2 mo.	Died	Born at home—uncomplicated
g	8 wk.	F	"Spontaneous"	—	Right	13 da.	Recovery	
h	9 wk.	M	? Dry cough	3 wk.	Left	3 da.	Recovery	
22	9 wk.	F	Convulsive seizure	10 da.	Right	5 da.	Recovery	
i	5 mo.	F	Fall from bed; rt. chest injury; no fracture	3 wk.	Right	3 wk.	Unknown	
j	9 mo.	M	"Hard cold" and probable pneumonia	6 wk.	Right	17+ mo.	Unknown	Still accumulating chyle at time of report
k	9 mo.	M	"Spontaneous" (influenza with "distressing cough")	25 da.	Right	1 wk.	Recovery	
l	13 mo.	M	"Spontaneous" (pneumonia)	(10 da.)	Right	9 da.	Recovery	
m	18 mo.	F	"Spontaneous" (bronchitis)	(3 wk.)	Right (later, bilateral)	2 mo.	Recovery	Developed flaccid paralysis of uncertain etiology. Follow-up for 6 yr. revealed no recurrence of chylothorax but paralysis persisted
8	2 yr.	F	"Spontaneous"	—	Right	7 wk.	Recurrence in 3 mo. Eventual recovery	No history of trauma or associated disease
n	2½ yr.	M	"Spontaneous"	—	Right	11 da.	Recovery	Abdominal pain and fever 10 da. Fever, cough, dyspnea shortly before chylothorax developed

o	4½ yr.	M	Fall down stairs	1 mo.	Left	1 mo.	Recovery	
p	5 yr.	M	—	—	Right	17 da.	Recovery	Intermittent dyspnea for several months before
q	6 yr.	F	Crushing chest injury, no fracture	‡	Left	7 wk.	Recovery	
r	9 yr.	F	Fell against window sill—no fracture	6 da.	Right	11 da.	Recovery	
s	9 yr.	M	Fall with crushing injury to chest; no fracture	3 da.	Right	1 mo.	Recovery	
t	10 yr.	M	Kicked by horse in sterno-clavicular area; no fracture	5 da.	Bilateral	8 da.	Recovery	
u	10 yr.	M	Struck in left infraclavicular area; fracture left first rib	—	Left	3 mo.	Recovery	Pack in neck
11	14 yr.	M	Fall on chest	4 da.	Right	21 da.	Died	Pneumoperitoneum; phrenic crush

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*The inciting cause listed here is that given by the respective authors.
†The latent period is taken from the time of trauma to the time of onset of definitive major symptoms or signs.
‡Not able to determine latent period from the report, but it was probably short. Child had respiratory distress on admission, and x-rays on admission revealed evidence of left pleural effusion.

TABLE II. CASES OF TRAUMATIC CHYLOTHORAX IN PEDIATRIC AGE GROUP SECONDARY TO INTRATHORACIC SURGERY

REF.	AGE	SEX	PREVIOUS OPERATION	SITE	LATENT PERIOD	DURATION	TREATMENT	OUTCOME
28	4½ mo.	M	Anastomoses of subclavian and pulmonary arteries for tetralogy of Fallot	Right	13 da.	4 da.	Ligation at site of leak	Recovery
*	?6 mo.	F	Reoperation for double aortic arch with removal of segment of aorta		7 da.	10 da.	Low ligation of duct through right chest	Recovery
28	12 mo.	M	Anastomosis of aorta and pulmonary artery for tetralogy of Fallot	Left	14 da.	3 da.	Ligation at site of leak	Recovery
This paper	2½ yr.	M	Exploration of heart and great vessels	Right	1½ da.	28 da.	Conservative therapy. Small amount drainage	Recovery
This paper	$6\frac{11}{12}$ yr.	F	Patent ductus closure	Left	1½ da.	9 da.	Ligation of major anomalous left-sided channel at site of leak	Recovery
29	10 yr.	F	Blalock operation	Left	3 da.	2 wk.	Ligation at site of leak	Recovery

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TABLE III. DOUBTFUL OR INCOMPLETE CASES* OF TRAUMATIC CHYLOTHORAX

REF.	AGE	SEX	INCITING CAUSE	LATENT PERIOD	SITE	DURATION	OUTCOME	REMARKS
a	8 wk.	M	"Spontaneous"	—	Right	17 da.	Recovery	Lymphangiectasis elsewhere
b	6 mo.	?	Pertussis	—	—		—	
c	3 yr.	F	Associated with (? chylous) pericarditis with compression of thoracic duct and right pneumonitis. Relieved by puncture	9 da. before				
d	3 yr.	M	Fall 2 mo.	?	Right	4 mo.	(Chyle still accumulating at time of report)	Probably tuberculous: fever, positive tbc test
e	3 yr.	F	? Injury	?	Right	6+ da.	Recovery	Fever, strongly positive tbc test but chest x-ray revealed no evidence of tuberculosis. X-ray Rx.
f	3½ yr.	M	(Swallowed button)	6 mo. with insidious symptoms	Right	(6 mo.) + 1 mo.	Recovery	Fluoro.: No evidence foreign body. Fluoro. 1 yr.: recovery
g	7½ yr.	F	(Apical catarrh, left lung)	(2-3 mo.)	Bilateral	14 mo.	Recovery	Tbc. negative, subsequent course entirely normal
h	8 yr.	F	"Trauma"	No other details given				

*Cases here are those in which there is reasonable doubt of a traumatic etiology or on which there is incomplete information.

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Etiology.—Cases of chylothorax may be divided into the traumatic group, in which there is a positive history of trauma; the nontraumatic group, in which there is intrinsic disease of the thoracic duct; and the "spontaneous" group, in which there is no history or evidence of trauma or intrinsic disease. The latter is limited almost exclusively to infants, although two cases recently were reported in adults.[1, 2] In this report, nontraumatic cases have been excluded.

Traumatic chylothorax may occur in either closed or open wounds of the chest. In a recent compilation of sixty-six cases of all ages by Hoffman and associates,[3] crushing injuries to the chest accounted for eighteen, and penetrating injuries for fifteen, whereas falls, blows on the chest, hyperextension of the spine, auto accidents (especially those in which the patient is thrown against the front seat), and severe coughing accounted for lesser numbers.

Of the thirty-two pediatric cases in this series (Table I), fourteen were traumatic, twelve were "spontaneous," six resulted directly from previous surgery. Eight of the twelve "spontaneous" cases occurred in children under one year of age and represented the majority of the cases in this age group. Two of the remaining patients under one year had probable birth trauma, whereas the other four cases were attributable to a previous fall, a convulsive seizure, a "hard cold" with pneumonia, and a "dry cough." In the age group 1 to 14 years, four cases were spontaneous; however, two of these had accompanying respiratory infections. The remaining eight cases were clearly traumatic.

Surgical accidents received no mention until Lampson's[4] review in 1948. Since then, an increasing number of cases have been reported, principally in adults,[5] attributable to previous surgery. We have found four pediatric cases secondary to surgery. These, with the two patients reported in this paper, bring the total since 1949 to six cases. These cases are summarized in Table II.

The etiology of "spontaneous chylothorax" is not definitely known. A number of authors suggest that birth trauma, particularly hyperextension of the spine, is important in producing rupture of the duct.[6] Others have postulated that overly vigorous resuscitation, strenuous coughing, or violent crying are contributory—presumably by altering pressure relations in the duct system.

Autopsy examinations by several authors allegedly failed to reveal the thoracic duct in infants dying of chylothorax. Bierman and associates[7] found it very difficult to locate the thoracic duct in adults unless cream was administered shortly before death. If congenital absence of the thoracic duct does occur, chylothorax should not result unless there is a rupture of collateral channels. The lack of evidence for an intrauterine effusion in any of the reported cases implies that intranatal or postnatal factors are important in the production of "spontaneous" chylothorax. In patients who had recovered, there has been only one reported recurrence[8] of "spontaneous" chylothorax.

Considering these factors, and the latent period of at least four days following birth in all cases of neonatal

chylothorax, we feel that most of these cases are traumatic in origin. Apparently major trauma is not necessary; other factors undoubtedly are important and one of these factors may be the anomalous structure of the duct system. Blystad and Wergeland,[8] on the basis of metabolic studies, advanced a different explanation for their "spontaneous" case; that a filtration mechanism rather than rupture of the duct may be responsible.

Signs and Symptoms.—Chylothorax is characterized by a sudden onset of dyspnea, tachypnea, a shocklike picture, and sometimes cyanosis. These symptoms result from the rapid accumulation of chyle in the intrapleural space with compression of the lung and a shift of the mediastinum. An equally distinctive finding is the rapid clearing of all symptoms after thoracentesis, though recurrence of symptoms with reaccumulation of chyle is usual. Physical findings are those of any pleural effusion. The fluid is odorless, has a milky appearance and a slightly alkaline reaction. The specific gravity usually is greater than 1.012. Chyle is bacteriostatic,[4] and is sterile on culture, which correlates with the rarity of empyema complicating chylothorax.

Microscopic examination reveals many very fine fat globules and a variable number of cells, mostly lymphocytes. In the early neonatal period the fluid may lack the milky appearance and be an orange-yellow color, which has been ascribed to the presence of a lactochrome pigment.[9] Sakula[10] noted that the atypical chyle obtained shortly after birth changed to the milky type with the institution of full milk feedings. Florer and Ochsner[11] described a transformation of typical chylous fluid to a straw-color fluid when their patient was placed on a fat-free diet. These observations suggest that the fat content is important in determining the color of the fluid.

After repeated thoracenteses for the relief of respiratory embarrassment, a new group of symptoms appear, which are related to nutritional depletion from the loss of the nutrients of the chylous effusion. Chyle contains approximately 3 to 4 Gm. per cent fat and 3 Gm. per cent protein, and its rate of flow varies between 60 and 190 c.c. per hour. Hence, losses of foodstuffs may achieve major proportions as exemplified by the 17-year-old patient of Little and co-workers[12] who lost 180,000 c.c. of chyle over a period of six months.

It has been noted that the right thorax is more often affected than the left, except in cases of penetrating injuries when the left side is more likely to be involved.[13, 14] A right-sided effusion is more likely to occur in injuries which are low in the thorax; injuries higher in the chest usually cause left-sided involvement.[15] This distribution is explained largely by the anatomical course of the thoracic duct through the chest.

Of the cases reviewed in Table I, there is a preponderance of right chylothorax (65 per cent). Left chylothorax prevailed among the cases secondary to chest surgery, probably because of the proximity of the duct to the great vessels in the left chest.

Latent Period.—In traumatic chylothorax there is a characteristic latent period between the injury and the stage of major symptoms. Baldridge

and Lewis[5] report an average latent period of two to ten days, although a case reported by Beatty[16] was said to have had a latent period of 6½ years!

In most instances, the explanation of the latent period is that the chyle originally escapes into the retropleural space and only secondarily penetrates the pleural space, where it attracts attention. Such a hypothesis receives support from those cases in which a retropleural effusion has been observed, as well as in those cases in which a communicating effusion between the retropleural and pleural spaces has been demonstrated.[15, 17-20]

Diagnosis.—The diagnosis of chylothorax may be made by aspiration of typical fluid and confirmed by the use of lipophilic dyes (Sudan III, D and C green), fed by mouth and recovered later in the aspirate.[21, 22] The nature of the effusion also may be identified by isotopic methods using deuterized fat.[23] All cases should be studied carefully for the possibility of intrinsic disease of the thoracic duct.

Mortality.—In the fifty-eight cases of all ages collected by Lampson,[4] the mortality was 45 per cent. Among the pediatric cases (Tables I and II), the mortality is much lower. Of the fourteen patients in the first year of life, there were four deaths; of the remaining twelve, ten recovered and the result in two cases is not definitely known. However, this is not a large series and there still is adequate reason to regard the condition as a serious one. One major reason for the unusually low mortality of this series is the short duration of the chylothorax —eighteen cases were of twenty-one days' or less duration, the remaining eight were over twenty-one days. Of the cases secondary to previous surgery (Table II), all patients except one were treated surgically and all recovered.

Treatment.—Until recently, treatment of chylothorax has been conservative. Of the many measures advocated,[5] none have met with any remarkable degree of success, as judged from the mortality statistics of Lampson.[4] In this series, repeated aspirations, together with attempts to maintain nutrition, have been most widely used.

In many cases the maintenance of adequate nutrition has been especially difficult.[12] Baldridge and Lewis[5] state that it is impossible to maintain adequate nutrition in the face of prolonged incontinence of the thoracic duct system. Oeken[24] first recommended the intravenous use of aspirated chyle as a contemporary replacement of loss, but its claims for rapid healing of the injured duct have not been borne out. Furthermore, the use of intravenous chyle is not without some danger as demonstrated in the cases of sudden death,[25, 26] and thrombophlebitis[11, 12, 27] following its use.

The use of conservative therapy was based on the surgical dictum that ligation of the thoracic duct in the chest was almost certainly fatal. Clinical and experimental evidence against this view has been adequately summarized in several reviews.[4, 5, 28]

Table II lists those cases in the pediatric group which have been treated by direct surgical attack on the duct system. Of the five patients subjected to surgery for chylothorax, all were successfully treated and there was no mortality. A number of adult

patients have also been treated surgically[4, 5, 26, 29-32] with but a single death[26] due possibly to a reaction to intravenous chyle rather than to the operation. Collectively, these results are very encouraging and make surgery the treatment of choice in chylothorax.

In view of the data presented there would seem to be some merit in waiting a short time for conservative measures, since collateral channels may open up.[33] However, one must balance this uncertain result against continuing nutritional depletion. With each thoracentesis, the operative risk becomes greater. Surgical intervention must be timed carefully and every possible measure taken in preoperative preparation. As Baldridge and Lewis[5] state: "It is our feeling that expectant and conservative treatment should be discarded within a reasonable time, before emaciation and cachexia supervene, and before the patient's condition is so extreme that major surgery is contraindicated."

Ligation of the lower thoracic duct should be effective in the treatment of most cases of left, and all cases of right chylothorax, regardless of etiology, *if* there are no major anomalous ducts. An alternate procedure in post surgical cases is the re-exploration of the previous operative site with an attempt to ligate the duct in the region of the leak. Administration of heavy cream or lipophilic dyes shortly before the operation may aid in visualizing the site of the leak.

Angiography of the thoracic duct system[34] may prove to be a valuable tool in the detection of major anomalies. To date, there have been no attempts at surgical treatment for "spontaneous" chylothorax in infants. This would seem to be a formidable surgical undertaking, but might be tried in cases which give no indication of spontaneous cure.

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COMPLICATIONS OF MYOCARDITIS IN CHILDREN

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MYOCARDITIS in children is not a rare disease. In a previous study, ninety-seven instances of myocarditis, which were encountered among autopsy material of 1,420 children, were described and analyzed.[1] Special attention was paid to the various diseases in which myocarditis occurs, its histologic characteristics, and clinical significance. In some of these instances the myocarditis was the major disease dominating the clinical picture and probably had been responsible for the death of the patient, while in others, myocarditis was a more or less serious complication in a primary disease and may or may not have contributed to the death of the patient at that particular time. It is difficult, if not impossible, to evaluate at autopsy myocarditis as *the* cause of death in cases where the inflammatory changes are neither diffuse, nor of a severe degree, nor involve portions of the conducting system. However, if it can be shown that the myocarditis had caused certain complications which per se are considered severe enough to be responsible for the death, it is also clear that myocarditis may then be regarded as the fatal disease. While there has been, during the last few years, a marked increase of reported studies on myocarditis, it is of interest to note that possible complications of this disease have not received any attention.

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This report concerns itself with a study of complications of myocarditis in children. Infants and children were selected because a larger relevant material was available, and also because taking the same number of blocks of tissues for study as in adults, relatively more tissues could be examined in children than in adults. For this study fifteen cases were chosen out of a series of forty-five instances of myocarditis in children who came to autopsy at Michael Reese Hospital between 1946 and 1952. In thirty of these forty-five cases myocarditis was associated with poliomyelitis eleven times, bacterial endocarditis four times, pyelonephritis three times, otitis media and mastoiditis three times, rheumatic fever, the Waterhouse-Friderichsen's syndrome, influenzal meningitis, and miliary tuberculosis twice each, and pancreatic disease once. It was thought that possible complications in these instances as found at autopsy could perhaps be attributed to the main disease rather than to the myocarditis. To avoid such a criticism, the remaining fifteen instances where the myocarditis was not associated with a disease known to cause myocarditis were chosen for study. Such a myocarditis by definition is classified as isolated myocarditis or Fiedler's myocarditis, and complications in these cases undoubtedly are related to the myocarditis itself. These fifteen cases were subjected to a careful histopathologic study involving most of the available

organs to determine what findings in organs other than the heart were associated with the myocarditis.

The ages of these children varied from 2 weeks to 13 years. Eleven were under 2 years of age. Seven were males and eight females. There were nine white and six Negro children. The clinical findings and the clinical diagnoses varied widely. Two children were diagnosed as having bronchial asthma. The others were thought to have anemia of undetermined origin, bronchopneumonia, septicemia, encephalitis, tonsillitis, diarrhea of unknown origin, congenital heart disease, intoxication or poisoning, hepatitis, and rheumatic heart disease, respectively. Three patients died in the admitting room. Their respective histories were as follows: The first (Case 6), a well-developed and well-nourished Negro infant, 2 months of age, was dead when brought to the emergency room. The mother stated that the baby was seemingly perfectly well until the evening before admission when she noted that he was listless, pale, and coughed occasionally. The second patient was an 18-month-old Negro boy (Case 8), admitted as an emergency. The child had been developing well and was never sick. Five days before admission the mother noted that he was "warm" to the touch. During the next few days he became listless and did not take food. On the day of admission the baby was cyanotic and had difficulties in breathing. He was acutely ill with stertorous and labored respirations. The temperature was 106° F., and the pulse rate 160 per minute. Intercostal retraction was noted. The pharynx was slightly hyperemic. The tympanic membranes were normal. The red blood count was 4,120,000 and the white blood count 34,000. The child died in the admitting room and no further laboratory data are available. The third child was a

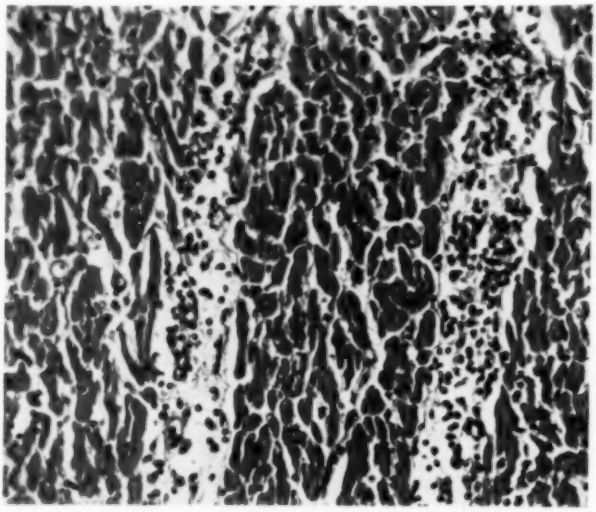

Fig. 1.—Principally interstitial myocarditis. (Hematoxylin and eosin stain, ×150.)

white male 1½ years of age (Case 14), who was brought to the admitting room in a terminal state. His skin was dry and warm. He had marked difficulty in breathing. Coarse râles were heard over both lungs. He died shortly after examination. The history disclosed that the child had been anorexic and listless during the past five days. On the morning of admission his face turned blue and he was gasping for air.

variety, but the muscle fibers were also often involved. In three instances outspoken foci of necrosis were encountered within muscle fibers (Cases 6, 8, 14). The most common inflammatory cells were polymorphonuclear leukocytes and lymphocytes. In five hearts a serous exudate predominated. Degenerative changes in muscle fibers were common.

Table I shows the type of changes found other than myocarditis, and how

TABLE I.

CASE	AGE	SEX	COLOR	DILATATION OF HEART	MURAL THROMBI	CORONARY EMBOLI	PULMONARY EMBOLI	PULMONARY INFARCTS	BRAIN EMBOLI	CLOUDY SWELLING OF PARENCHYMATOUS ORGANS	PASSIVE HYPEREMIA	EDEMA OF LUNGS
1	1½ yr.	F	W				+			+		
2	3 yr.	F	W		+	+				+	+	+
3	5 mo.	F	W	+						+		+
4	2 yr.	F	W	+						+		+
5	9 mo.	F	W				+			+	+	+
6	2 mo.	F	N			+	+				+	+
7*	2 yr.	F	W						+	+		
8	1½ yr.	M	N			+	+			+	+	
9	23 mo.	M	N	+			+	+	+		+	+
10	3 mo.	M	N				+		+	+	+	+
11	7 wk.	F	W	+						+	+	+
12	9 yr.	M	N	+	+		+	+	+	+	+	+
13	13 yr.	M	N		+				+		+	+
14	1½ yr.	M	W			+	+					+
15	5 yr.	M	W			+				+		+

*Emboli were also found in the pancreas and in a lymph node.

At autopsy, in none of these fifteen patients was there found any disease which is sometimes associated with myocarditis. Myocarditis was suspected on gross examination nine times because of the flabbiness of the heart, the gray color and moisture of the cut surface of the myocardium, and because the normal architecture was obscured. Microscopically the myocarditis was verified in every instance. It was predominantly of the interstitial

often such changes were found. It also shows the incidence of edema of the lungs, of passive hyperemia of the various organs, and the frequency of cloudy swelling in the parenchymatous organs.

Outstanding and completely unexpected were the findings of emboli in the coronary arteries, the pulmonary arteries, and in arteries of the brain. All of these were bland emboli. Emboli were found in the coronary arteries

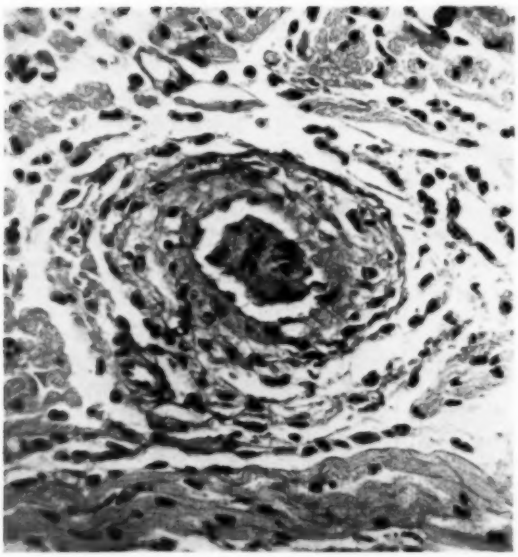

Fig. 2.—Embolus in branch of coronary artery. (Hematoxylin and eosin stain, ×200.)

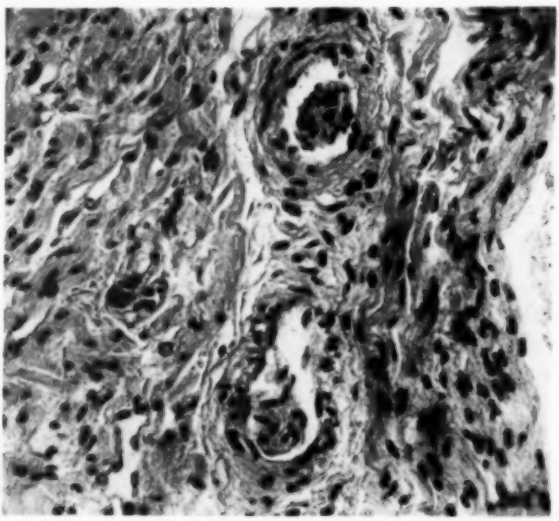

Fig. 3.—Embolus in branch of coronary artery. (Hematoxylin and eosin stain, ×225.)

five times, in the pulmonary arteries eight times, and in the brain five times. These emboli were not seen grossly, but were encountered only on microscopic examination of the various organs. The involved vessels were small arteries not showing any changes of their walls. The emboli consisted mainly of accumulations of red and white blood corpuscles with a small amount of fibrin. More rarely were hyaline or so-called fibrin emboli noted. Attempts at organization were not seen. Confirming that they were emboli rather than thrombi were the facts that they were often multiple, that there were no changes in the walls of the involved vessels, and that in those instances where mural thrombi were seen on the endocardium, the emboli greatly resembled those thrombi.

The sources of these emboli were most likely mural thrombi in the heart, even though in this series mural thrombi were found only three times. However, these thrombi were not seen on gross examination of the heart, but were discovered only by chance in sections of the myocardium and adjacent endocardium. We believe that if the whole hearts had been available for examination at the time this study was undertaken, thrombi would have been found in more hearts. Further, the fact that there were often emboli in several organs, points to the heart as the site of origin of the causative thrombi. The cause of the thrombi is obviously the myocarditis, the inflammatory changes close to the endocardium producing subendocardial edema, or even localized foci of mural endocarditis predisposing to the formation of thrombi. Their origin is probably quite similar to those adjacent to myocardial infarcts. Tedeschi and Stevenson[2] remarked on the involvement of the mural endocardium in their cases of interstitial myocarditis in children. However, our study of the three cases in which the mural thrombi were found did not provide sufficient information as to their exact cause.

Coronary emboli were found in five instances. While such emboli arising from vegetations of the various bacterial endocarditides are common, emboli arising from thrombi are rare. In Hamman's[3] series there were five instances where the source of the coronary emboli could be traced to intracardiac mural thrombi. It is interesting and perhaps significant that in the three patients who died in the admitting room, and whose histories were previously given, coronary emboli were found. It seems clear that the additional impairment of the heart already handicapped by the myocarditis was sufficient to have caused the rather quick death of these three children. The emboli were obviously too recent to have caused myocardial infarcts.

Pulmonary emboli were encountered eight times. In two cases emboli were found only in the lungs. In the other six cases emboli were also present in other organs. Since the foramen ovale in all these hearts was either closed, or only probe patent, the emboli most likely arose from thrombi in the right atrium or the right ventricle. Yet, as stated, mural thrombi were actually demonstrable in only three hearts. Pulmonary infarcts were also present in *two* of these cases. While it is true that one pulmonary embolus does not cause infarction in a lung in the absence of chronic passive hyperemia because of the rich blood supply of the lungs, multiple emboli will cause infarction. Both of these children had

clinical evidence of lung involvement interpreted as broncho-pneumonia. One patient, a 9-year-old Negro female, had been diagnosed as having acute rheumatic pancarditis, while the autopsy disclosed no evidence of a rheumatic infection, but did reveal isolated myocarditis (Case 12).

Emboli in small arteries of the brain were present in five instances. Permission to examine the brain was obtained only in eleven of the fifteen cases. In only one instance were foci of subarachnoid hemorrhage found. The brains of the other four children showed various degrees of hyperemia, but there was no other evidence of brain involvement. Some of the clinical findings in four of these children may be significant. A 13-year-old Negro boy (Case 13) developed convulsions on the morning of admission, followed by coma. A 2-year-old white girl (Case 7) was admitted with convulsions and dilated and fixed pupils, and a 23-month-old Negro boy (Case 9) was admitted with fever and convulsions. This patient also had a pulmonary infarct. A 3-month-old Negro male infant (Case 10) became markedly dyspneic and lethargic on the second day of admission and died the next day. The above-mentioned foci of subarachnoid hemorrhage were found in this instance. It should be emphasized that a careful examination of the brains disclosed no evidence of encephalitis. This especially so, since it was first thought possible that the myocardial changes and the clinical evidence of possible brain involvement might speak for so-called encephalomyocarditis.[4]

One of the children with cerebral emboli also disclosed emboli in the pancreas and in one of the lymph nodes in the absence of any significant changes in these structures (Case 7). While these findings per se probably are of no importance, they may indicate that perhaps a greater number of emboli in various organs might have been found if more tissue had been examined microscopically.

So far as the cause of the myocarditis in these instances is concerned, we have little to offer. Since the autopsies did not disclose any disease which may be complicated by myocarditis, and because the myocardium was the only involved structure in the heart, the myocarditis falls under the classification of isolated or Fiedler's myocarditis. None of the children had received any medication which is known to cause hypersensitivity prior to the onset of the final illness. There also were no blood vessel changes or eosinophils in the region of the myocarditis. The inflammatory exudate in the absence of any granuloma was also not characteristic of any specific infection. Noteworthy were the foci of necrotic muscle fibers encountered in three instances as had been mentioned before. We have repeatedly noted small or minute foci of necrotic heart muscle fibers accompanied by a nonspecific inflammatory reaction in viral diseases, and it is thus possible that the myocarditis in these three instances might also have been caused by a virus, although we have no other demonstrable evidence.

From this study it is clear that mural cardiac thrombi and, in particular, multiple emboli are relatively frequent complications of myocarditis in children. From our observations it is also obvious that these are serious complications contributing to the death of some of these patients. The

findings suggest that the use of anticoagulants in such patients might contribute to their recovering on the basis that the anticoagulants may prevent the formation of the mural cardiac thrombi and consequent emboli. On the other hand, if the clinical diagnosis of myocarditis were made earlier and conventional methods of therapy used, the occurrence of these complications may even more safely be prevented.

SUMMARY

This study was undertaken to ascertain what, if any, complications may arise in instances of myocarditis. Infants and children were selected because larger relevant material was available. Since it was important to ascertain that possible complications were actually caused by the myocarditis per se and not by a primary infectious disease which originally may have caused the myocarditis, only cases of isolated (Fiedler's) myocarditis were used for the study. Of forty cases of myocarditis observed during the last eight years, fifteen fulfilled the criteria of isolated myocarditis. Outstanding were the findings of minute emboli in the coronary arteries and cerebral vessels. The sources of these emboli apparently were small mural thrombi in the heart, although these were found only in three cases. These thrombi were discovered by chance in the available section of the myocardium and adjacent endocardium. It is possible that more thrombi would have been demonstrated if more tissues had been available at the time of this study. The fact that often multiple emboli were present in several organs, speaks for the heart as the source of the emboli. The cause of these emboli is obviously the inflammatory changes close to the endocardium producing subendocardial edema or even localized foci of mural endocarditis predisposing to the formation of thrombi. From an analysis of the relevant case histories it seems quite clear that multiple emboli constitute a serious complication contributing to the death of the patients.

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CONGENITAL GOITER WITH EXOPHTHALMOS AND HYPERTHYROIDISM

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IN REVIEWING the literature one finds that hyperthyroidism below one year of age is a curiosity, but at birth a rarity. Klaus[1] reported a case which developed at age 9 months, Altman[2] one at 3 months, Helmholz[3] one at 11 months, Elliot[4] one at 6 months, Ellis[5] one at 4½ months, Osehsner[6, 7] one at 5 weeks, Frisk, and Josefsson[8] one at 2 months, Margetts[9] one at 1 month, and Fischer[10] one at 6 days. White[11] in 1912 described the first case of congenital hyperthyroidism. In his case the mother developed classical hyperthyroidism during the fifth month of pregnancy and supposedly delivered at term. The baby's weight was 2,000 grams and presented all the classical signs and symptoms of Graves' disease. White states, "The eyes were staring and proptosed, and the thyroid was uniformly enlarged. The cardiac rate could not be counted, and there was a loud murmur over the entire precordium. The temperature was 99° F. The child remained quite cyanosed. The child died thirty-five hours after birth."

I believe the following case is the second report of congenital hyperthyroidism and the first report of an infant who has lived.

In the three[9, 10, 11] cases of hyperthyroidism reported in the neonatal period the mothers have all been hyperthyroid. This case differs in that the mother was hypothyroid.

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CASE REPORT

This white female infant was born at St. Louis Maternity Hospital, Feb. 19, 1953. The mother, aged 27, was gravida ii, para i. She developed signs and symptoms of hyperthyroidism at the age of 18, shortly after the birth of her first child who is a male and in excellent health. Three years later a thyroidectomy was performed at Walter Reed Hospital, Washington, D. C. Preoperatively the basal metabolic rate was plus 110. She did well for about one year when signs of toxicity recurred. At this time the basal metabolic rate was plus 36. She was studied at Barnes Hospital, St. Louis, where a diagnosis of substernal thyroid was made. Radioactive iodine was given. All signs of toxicity disappeared and the basal metabolic rate on one occasion was reported 0, –3. In March, 1952, a dilatation and curettage with cervical conization was performed because of menorrhagia. In July, 1952, she conceived. During the fifth month of pregnancy the basal metabolic rate was –14, and 60 mg. of thyroid daily was prescribed during the remainder of the pregnancy. Although the mother has marked exophthalmos, she was and is operating at a hypothyroid level. The basal metabolic rate on the seventh postpartum day was +1, –2. Two and one-half months later the basal metabolic rate was reported as –30. The paternal grandmother had an operation for a nontoxic goiter, and two aunts and one uncle, both on the paternal side, have been treated for some type of thyroid dysfunction without surgery.

The baby was born after an estimated twenty-eight-week gestation. Birth weight was 1,550 grams and the length 40 cm. The mother's mem-

branes had ruptured seventy-two hours prior to delivery. Only Trilene was given for the actual delivery. Presentation was cephalic. Because of sluggish initiation of respiration the child was placed in the Air Lock and cycled for ninety minutes at 1 to 3 pounds of pressure. Immediately after birth the nutritional state was considered good for a baby this size. The skin was warm, moist, and very flushed. The baby was very restless and fidgety. Clonic movements of the extremities were noted. Marked bilateral exophthalmos and puffiness of the eyelids were present. There was no bulbar pulsation and the intraocular tension appeared normal. The thyroid gland was markedly enlarged, soft, and the right lobe was larger than the left. No bruit or thrill was noted. The pulse was 190 to 200 per minute, and the respiratory rate 120 to 130 per minute. It was thought that the heart was slightly enlarged to the left. A soft systolic murmur was heard over the entire precordium. Blood pressure by the flush method in the right leg was 90 mm. Hg. Good femoral pulsations were present. There was moderate subcostal and suprasternal retraction. Aeration was considered only fair. Fine atelectatic râles could be heard over both bases anteriorly. The liver was firm, had a sharp edge, and was at the level of the umbilicus. The spleen was down 2 to 3 cm. below the costal margin.

The child was moderately atelectatic and appeared to be in thyrotoxic crisis and early heart failure.

After removal from the Air Lock the baby was placed in an Isolette with continuous oxygen and the head was placed in a position of hyperextension to alleviate pressure symptoms. Lugol's solution, two drops every eight hours, digitalis, penicillin, and streptomycin were started. The capillary whole blood true glucose eight and one-half hours after birth was 0 mg. per cent. The baby was given 5 c.c. of a 10 per cent fructose solution every two hours by polyethylene nasal tube. Later on the day of delivery a lactose-fructose mixture 6 c.c. every hour was given. Because the above feedings had been well tolerated and it was thought imperative to supply adequate calories, a formula of 20 Gm. of Alacta and 120 c.c. of a lactose-fructose diluent was started at approximately 18 hours of age. Forty-eight hours after birth the formula was increased to 38 Gm. of Alacta to 150 c.c. of the lactose-fructose diluent, and 12 c.c. was given every two hours. Seventy-two hours after birth a 1:2 Alacta formula with 5 per cent Dextri-Maltose No. 1 was given in 15 c.c. feedings every two hours. Capillary whole blood true glucose taken twelve and one-half hours after delivery was 53 mg. per cent and on the fourth day was 73 mg. per cent. The baby remained on the Alacta formula for the remainder of hospitalization, with gradual increases in the quantity and lengthening of the interval to three hours. By the thirteenth day of life feedings were given by mouth. Digitalis was discontinued on the eighth day, and antibiotics on the third day of life. Lugol's solution was decreased to one drop every eight hours on the eighth day, on the thirty-first day to one drop daily, and discontinued on the forty-second day of life.

On the second day of life the cardiac rate dropped to 160 to 170 per minute and the respiratory rate to 100 per minute. The systolic murmur was more apical and of greater intensity. The child was still very flushed, jumpy, and restless. By the third day the thyroid was smaller, the degree of exophthalmos had decreased slightly, and the liver and spleen were slightly smaller. There was no change in the character and localization of the murmur. The pulse was 160 to 170, and the respiratory rate 100. On the fifth day the baby appeared more comfortable; all jumpiness and restlessness had disappeared. The pulse was 140 to 150 and the murmur persisted. The degree of exophthalmos and thyroid enlargement continued to slowly diminish. By the ninth day the murmur had disappeared and the pulse

Fig. 1.—Infant at one day of age.

Fig. 2.—Infant at 7 months of age.

Fig. 3.—Infant at 11 months of age.

was 120 to 130. The liver still remained firm, 2½ cm. below the costal margin. Initially the weight gain was slow but steady and on the twenty-third day the baby weighed 1,800 grams. Birth weight had been 1,550 grams. In the next ten-day period the weight gain was more rapid, and on the thirty-third day the weight was 2,110, forty-third day 2,560, and on discharge five days later 2,730 grams. The temperature course was perfectly normal during the entire hospitalization with the exception of one reading of 36.2° C. about eight hours after birth. At this time the capillary whole blood true glucose was 0 mg. per cent. At one month the cardiac rate was still 120 to 130 per minute, respirations 65 to 70 per minute, the degree of exophthalmos and thyroid enlargement had continued to decrease slowly, but the liver remained firm 2½ cm. below the costal margin. The baby was discharged on the forty-eighth day. He weighed 2,730 grams, was 47.7 cm. in length, and had a respiration and pulse of 50 and 120 per minute, respectively.

Laboratory Data.—The initial complete blood count at one day of age was: erythrocyte count 5.74 million per cubic millimeter, hemoglobin 18.7 Gm. per cent, leukocyte count 18,250 per cubic millimeter with 1 per cent eosinophils, 8 per cent stabs, 49 per cent segmented, 36 per cent lymphocytes, and 6 per cent monocytes. Subsequent blood counts were also not remarkable. The initial urinalysis at one day of age was pH 5, albumin, sugar, and microscopic examination negative. Just before discharge report on a urinalysis was pH 5, specific gravity 1020, albumin and sugar negative, and on microscopic examination only an occasional erythrocyte and leukocyte. Capillary whole blood true sugars were 0 mg. per cent eight and one-half hours after birth, 53 mg. per cent four hours later, and on the fourth day 73 mg. per cent. Microblood cholesterols were 99 mg. per cent on the fourth day, 146 mg. per cent on the twenty-seventh day, 161 mg. per cent on the thirty-fourth day, and 183 mg. per cent on the forty-sixth day of life. Protein bound iodine and radioactive iodine uptake were not done because of the precarious clinical status of the patient. An x-ray film of the entire body in an antero-posterior view was done on the forty-eighth day of life. This revealed "Bony structure as visualized appears normal. There are two centers of ossification in the wrist. There is a large superior mediastinal mass extending both to the right and left. The mass seems smaller at the thoracic inlet and probably represents enlarged thymus. A substernal thyroid cannot be ruled out, however."

At 9 weeks of age the baby weighed 3,330 grams and measured 49.5 cm. in length. The weight gain and linear growth were adequate at all the subsequent examinations. The weight was 8.070 grams and the length 68.6 cm. at age 11 months, representing a weight gain of 6,520 grams and a linear growth of 28.6 cm. since birth. At 9 weeks the pulse was still a little rapid, 100 per minute, but thereafter the pulse was considered normal. The hepatosplenomegaly had disappeared by the sixteenth week. By the ninth week the eyes were only slightly proptosed, and both lobes of the thyroid had shown a remarkable decrease in size, but the isthmus showed no appreciable change. At 12 weeks the thyroid was thought to be generally smaller, but the exophthalmos remained the same. By the sixteenth week the thyroid enlargement had completely disappeared, but the eyes remained slightly proptosed. All exophthalmos had disappeared by the twentieth week. The child was "colicky" for the first four months of life. By the fourth month the child was cooing. She sat at the age 7 months, and by 9 months was pulling up to the standing position. At the eighth month she suddenly developed an alternating strabismus. Because of this she was referred to an ophthalmologist who also noted a marked myopia. At 11 months, because of the myopia, glasses were attempted. Ac-

cording to the parents the child has been in a new world since. By the eleventh month two lower central incisors had erupted.

DISCUSSION

In discussing this case of congenital hyperthyroidism in a child born of a mother in a hypothyroid state, several basic principles must be considered.[12, 13, 14]

First, the relationship of the anterior pituitary to the thyroid gland—the so-called "pituitary-thyroid axis." The two glands are normally in hormonal balance. The thyrotropic hormone of the anterior pituitary stimulates the thyroid to produce thyroxine, and this in turn inhibits the anterior pituitary in the production of thyrotropic hormone.

Second, according to animal experimentation, the probable actions of the thyrotropic hormone on the thyroid gland are: activation of the proteolytic enzymes, release of thyroxine, hypertrophy of the thyroid cells, increase in the uptake of iodine, hyperplasia of the gland, and increase in the production of thyroid hormone.

Third, the general principle in endocrine physiology that when a gland is removed for which there is a tropic hormone, the gland producing the tropic hormone hypertrophies and becomes hyperactive.

With these three considerations in mind one might explain why this baby born of a mother in a hypothyroid state had the classical picture of hyperthyroidism at birth.

The mother was on thyroid 60 mg. daily for the last two months of pregnancy. Instead of operating at the usual hyperthyroid level during pregnancy she remained in a hypothyroid state. During the fifth month of pregnancy the basal metabolic rate was −14, and basically was probably lower because of the history of thyroidectomy and later treatment with radioactive iodine. Because of the decreased thyroid function the maternal anterior pituitary was stimulated to secrete excessive amounts of the thyrotropic hormone. This in turn stimulated the fetal thyroid to a state of toxicity.

A case reported by Keynes[15] in 1952 adds clinical proof that the maternal thyrotropic hormone has the ability of passing the placental barrier and affecting the fetus. In this case a women aged 19 had a thyroidectomy for hyperthyroidism of moderate severity. A progressive exophthalmos developed following the operation. One year later she gave birth to a child who had congenital exophthalmos without any other signs of toxicity. The author states, "Here we see another example of hormone transmitted through the placental circulation. This time it is the thyrotropic hormone acting only on the infant's orbits—a clinical curiosity which has seldom if ever been observed before."

The above explanation considers only the abnormal stimulation of the fetal thyroid by the maternal thyroid-stimulating hormone, but two cases in the literature, one by Frisk, and Josefsson,[8] and the other by Fischer,[10] make one suspicious of some imbalance in the fetal thyroid-anterior pituitary balance. In both these cases signs and symptoms of hyperthyroidism in the babies developed after birth. Both mothers were hyperthyroid, and both had been treated during pregnancy with propylthiouracil. In these cases one cannot explain the development of hyperthyroidism in the neo-

natal period on the basis of excessive maternal thyrotropic stimulation on the fetal thyroid. Instead, overstimulation of the fetal anterior pituitary affords the most likely explanation. In these cases it is possible that the thiouracil drugs blocked the synthesis of fetal thyroxine, and in so doing caused excessive stimulation of the fetal anterior pituitary. Following birth the thiouracil inhibition to the infant's thyroid was removed, but the hyperfunction of the infant's anterior pituitary persisted, causing a transient hyperthyroidism.

In our patient with congenital hyperthyroidism born of a mother in a hypothyroid state, one needs only to consider the maternal thyrotropic stimulation of the fetal thyroid gland. With the present endocrinological concepts it would be difficult to explain how fetal thyrotropic stimulation played any part in this case.

Margetts[9] in 1950 reported a case of hyperthyroidism in the neonatal period along with a review of the literature. In this article six additional cases of hyperthyroidism in infants under one year of age were noted. Margetts states, "The notable feature of the published cases apart from that reported by White (1912) which died after thirty-five hours, is the benign course." Fischer[10] in his reported case, which had its onset at seven days of age, states, "Lugol's solution did not greatly influence the course of the disease." In our case it was evident that without supportive care, plus the use of Lugol's solution, we could not have saved the baby.

The severe hypoglycemia eight and one-half hours after birth can be explained on the basis of prematurity with its physiologic hypoglycemic state thought due to a poorly developed regulatory mechanism which creates a state of relative hyperinsulinism.[16] Also, the markedly increased metabolic rate with consequent exhaustion of all glycogen stores played a big part in the hypoglycemia. Perhaps, because of stress, there was some degree of transient adrenocortical insufficiency.

SUMMARY

A review of the literature revealed ten cases of hyperthyroidism in infants under one year of age. Even more unusual is its occurrence at birth. There was one previous report of congenital hyperthyroidism. This case, I believe, is the second reported and differs from the original case in that the mother conceived and delivered in a hypothyroid states and the baby lived. Because of the hypothyroid state of the mother, the hyperthyroid state in the baby was explained on the basis of stimulation of the fetal thyroid by excessive maternal thyrotropic hormone. Reports of thyrotoxicosis beginning in the neonatal period would lead one to believe that its course is quite benign. In this case of congenital hyperthyroidism, however, without good supportive care, and a good response to iodine therapy, the baby would not have lived.

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ERYTHRODERMA DESQUAMATIVA

Two Cases in the Same Family

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LEINER, in 1908, first described a skin disease in young infants resembling a severe type of seborrheic dermatitis. Reports of this disease are infrequent in the medical literature of this country but fairly common in the European literature. The etiology is unknown although an infective process is commonly mentioned. The following report is of two cases in the same family.

CASE REPORT

Family History.—The father is living and well, aged 39. He has three brothers and two sisters that are living and well. His brothers and sisters all have children but there is not another case of this disease.

A first wife died following the birth of their first child, in 1939. The wife had rheumatic heart disease but the exact cause of death is not known. The child died several hours after birth. The father remembers her as being very red. Hospital records are too inadequate to draw any conclusions and the attending doctor is dead.

The second wife is living and well, aged 41. She has two brothers and two sisters, living and well. Her parents are living and well. The brothers and sisters all have children who have no evidence of the disease.

K. B., male, was born April 12, 1951, after an eight-month pregnancy that was normal in every way. There were no illnesses of any type during the pregnancy. Birth weight was 4 pounds 12 ounces. The skin was erythematous, dry, and cracking. The child was eating well. On the fourth hospital day he was discharged.

First hospital readmission was on April 26, 1951, with a "skin rash." The mother noted that the skin became progressively worse at home despite the use of some telephone-suggested remedies. The physical examination disclosed an erythematous moist sealy rash over the head, face, neck, anterior thorax, and the anogenital area. Some of the areas were secondarily infected, some bleeding. The physical examination was otherwise normal. Treatment was with penicillin intramuscularly, Burow's solution, and heat locally. He improved and was discharged on April 30, 1951.

About forty-eight hours after release he developed a severe diarrhea. Within a few hours he became lethargic and refused feedings and was readmitted May 2, 1951. Admission physical examination showed some dehydration. The skin rash was much worse than on release three days earlier. The patient was treated with parenteral fluids, penicillin, and heat. The dehydration was corrected but the skin looked worse. The skin was diffusely erythematous, with crusts, weeping, and exudation. Generalized edema was also noted. The first heart sound was described as being roughened. The patient was placed on ACTH, potassium chloride, Olac formula, and penicillin. For the next five days hypothermia was a problem. The temperature remained about 94° F. (R) until the sixth day when it returned to normal. He began to eat well and to gain weight. However, on

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May 21 it was noted that he was losing weight despite a good appetite and normal bowel movements. He was placed on a Nutramigen formula which was refused and therefore given by gavage. The weight continued downhill. At this time a systolic apical cardiac murmur was noted but the physical examination was otherwise normal. On the morning of May 30, 1951, after the morning feeding the child very suddenly died. Permission for autopsy was denied. Clinical impression was (1) Leiner's disease and (2) possible congenital heart disease.*

P. B., female, was born Aug. 16, 1952. Birth weight was 6 pounds. The skin was red but there was no scaling. Temperature remained constantly normal. After four hospital days the baby was taken home, and with the exception of some diaper rash, the mother had no difficulty with the baby.

J. B., female, was born Feb. 19, 1954. Birth weight was 5 pounds 11½ ounces, and length, 18 inches. At birth the baby was cool and very red. She was placed in an incubator and given oxygen. She was first seen when she was about 5 hours old. She was extremely red with some blueness about the mouth. Her temperature rectally was 93° F., taken with a laboratory thermometer. The heat in the incubator was turned on high and hot-water bottles were placed around her. Oxygen was continued, cortisone 6.25 mg. was given every eight hours, and oral feedings of Olac were started. After about twenty-four hours her temperature rose to 97° F. but the extra heat had to be continued to maintain her temperature at or near that point. It took the infant about six more days before she was able to maintain a normal temperature without the aid of the hot-water bottles. Over the course of the first week the generalized erythema gradually faded, but some spots remained. Her scalp, face, neck, axillae, anogenital area, and three areas on her abdomen remained red. The abdominal areas rapidly darkened and ulcerated, forming one large and two small ulcers. Cortisone was stopped; penicillin intramuscularly and a bacitracin-neomycin ointment was used locally on the ulcers. After three days on this routine her condition became worse. The ulcers on her abdomen were secondarily infected, areas on her neck were oozing, and her weight was going downhill. The ointment was discontinued and Varidase soaks were started. Within twenty-four hours there was a dramatic improvement in the appearance of the ulcers and within another four days they were healing nicely. Loose stools appeared off and on and produced considerable irritation to the anogenital area. She now began to gain weight, slowly and irregularly, but by the end of the first month her weight was 6 pounds, 4½ ounces. During the first month there were four episodes of generalized peeling. Her skin would become dry, flake and peel off in small pieces, leaving a red base, which would gradually lighten only to become dry and peel again. At the end of the first month the redness was confined to her scalp and face. During the second month the scalp became a major problem with the formation of thick crusts. This was treated with a 5 per cent coal-tar ointment with very good results. Vitamin A and D ointment was used on the skin but it did not stop the process of peeling. At the end of two months she had four more peelings but her weight was 8 pounds 1 ounce. At the beginning of the third month a 2½ per cent hydrocortisone ointment was applied to the entire body in an attempt to stop the cycle of peeling. This worked very well and she stopped peeling entirely. She was discharged home on the Vitamin A and D ointment for her body, coal-tar ointment for the scales on her head, and hydrocortisone ointment in case the redness would reappear.

After three days at home the parent returned with the child. The

*Patient of Dr. Viola Startzman.

redness over the face, body, and head had reappeared. She had developed a watery nasal discharge and a cough. On physical examination there was some oozing about her neck, a pharyngitis, and some coarse râles in the right chest. The temperature was within normal limits. A chest film revealed that the right lower and middle lobes were involved in a pneumonic process; the chest otherwise was normal. Erythromycin suspension was given orally. The ointments that she had been on were all stopped and 3 per cent Vioform cream was used exclusively. In about forty-eight hours the skin began to clear. Over the course of the next ten days her chest gradually cleared, and her skin became clear, except that it was a little too dry, so the ointment form of Vioform was substituted. After her chest had cleared completely, her skin was clear, weight gain was good, and she appeared ready for discharge but she again developed a cold, this time with a nonsuppurative otitis media. This was again treated with erythromycin with good results. She was again released after about three weeks of hospitalization. Her weight was 11 pounds 13½ ounces. She was eating well.

COMMENT AND CONCLUSION

Erythroderma desquamativa is an unusual skin disease. To have it occur twice in one family is even more unusual. No definite etiology can be determined, but a familial aspect is suggested by this report.

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HYPOTONIA

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HYPOTONIA is a condition in which there is a diminution or loss of muscular tonicity in consequence of which the muscles may be stretched beyond their normal limits. Tonicity is a state of normal elastic tension.[1]

The term hypotonia was first used to describe a clinical entity in the early part of the twentieth century. A case was reported by Finkelstein[2] in 1916 of a 1-year-old child who showed an unusual mobility of virtually all joints of the body without any true muscular weakness. This child was born with lax joints of her extremities as well as the spine. The hips appeared chronically subluxated and could be dislocated and reduced at will.

In 1919, Jahss[3] reported a similar case of a child with hypotonia. Sobel[4] in 1926 reported on what he called essential or primary hypotonia in children. He listed various conditions in which muscular and joint hypotonia may be found.

Key[5] in 1927 reported two cases of hypermobility of joints in a family. He believed that this condition may occur as a congenital abnormality.

Michaels and Searle[6] related in 1933 a case of hypermobility of the joints with superimposed postencephalitic parkinsonism. Sturkie[7] in 1941 gave an account of hypermobile joints in all descendants for two generations. Sutro[8] in 1947 added five more cases to the literature where no similar involvement was noted in members of the immediate family; recurrent articular effusion of both knees and ankles was present. One patient had a mild laxity of the facial skin.

The etiological factor is unknown, but some authors believe it to be a sex-linked hereditary characteristic. The pathological process is as yet unknown. The condition may be due to an inherent laxity or redundancy of the ligaments or joint capsule. An endocrine disorder may be responsible; the relaxation of ligaments is a well-known fact during pregnancy.

The following have been described by the above authors: The presenting complaint is related to joint function so that the patient shows a retarded ability in walking and standing. There is difficulty in maintenance of balance. The spine may show increased lordosis. The patient demonstrates the phenomenon described by the laity as a "double-jointed" condition. The above findings are noted very early in life and they may vary in severity.

Examination reveals: (1) normal muscle power but poor tone, (2) normal reflexes present, (3) joint relaxation that may be to such a degree that subluxation or dislocation is present, (4) hypermobility which varies in degree, (5) electrical studies normal, (6) bone that is inherently normal.

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Laboratory studies are essentially negative. The prognosis is favorable in that there is a gradual improvement. This is especially so if an effort is made to maintain the joints in a functional position.

CASE REPORT

A white female, 16 months of age, was referred to the Research and Educational Hospitals because of "multiple deformities of the extremities" noted since birth. She was the fourth in a family of five children. The others were normal. There was no positive family history for hypotonia. Delivery was normal. According to the original hospital records, she was born with a condition known as "hyperextensibility of both legs." At that time, gradual correction of the deformity was advised by use of plaster encasements. However, this was carried out only two weeks.

Positive findings showed an alert cooperative white female. The skin about the lower abdomen, thighs, and knees hung in folds, and there was increased elasticity. This condition was minimal in the upper extremities. There was a diffuse plexiform-like mottling, spider-web-like in pattern suggesting a cutis marmorata.

She could only stand when supported. The feet showed moderately severe pronation, and the knees, hyperextension. The patient could sit by herself, but with marked dorsal rounding. On lying down, the abdomen bulged at the rib margin.

The legs were maintained in about 20 to 25 degrees of abduction, 70

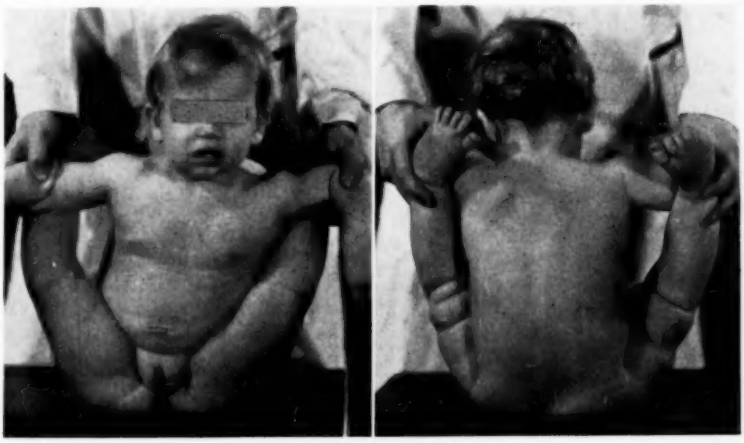

Fig. 1. Fig. 2.

Figs. 1 and 2.—This posture was maintained with ease.

Fig. 3.—Note the bilateral genu recurvatum

degrees of external rotation, and about 15 to 20 degrees of flexion. She could move the lower extremities in all directions. When she did this, the knees went into 10 to 15 degrees of hyperextension and the legs swung about as one unit without bending of the knee.

Leg lengths and circumferential measurements were equal. The right arm showed increased circumference as compared with the left.

Joint motion was as follows:

	Right	*Left*
Hip	*(Degrees)*	*(Degrees)*
Flexion (knees touched bed sheet)	180	180
Adduction	90	90
Abduction (feet touched ears)	180	180
Internal rotation	90	90
External rotation	100	100
Extension	40	40
Knees		
Flexion	Complete	Complete
Extension	215	215

Both knees subluxated in extension —the right more than the left. The right knee maintained itself usually in hyperextension.

Feet	*(Degrees)*	*(Degrees)*
Abduction	30	30
Adduction	25	25
Varus	45-50	45-50
Valgus	35-40	35-40
Equinus	70	70
Calcaneous	65-70	65-70

Hypotonia was present particularly in the lower extremities. Neurological changes were absent. Movements of hips and knees were cumbersome because of the hypermobility.

X-rays of the knees showed bilateral subluxation. In extreme phases of hip motions, there was no displacement of the femoral heads. There was a thickening of the subcutaneous layer, especially in the lower extremities. The bone age and the chronological age were compatible.

Clinical laboratory findings were essentially negative. Electromyographic studies showed no reaction of degeneration. The action potentials were normal.

A biopsy was done in the left thigh area so that a portion of skin, subcutaneous tissue, fascia, and muscle was removed. An elliptical incision measuring approximately 2 to 3 cm. in length was made on the lateral aspect of the left thigh, the excision including subcutaneous fat. A portion of the underlying tensor femoris muscle and its musculotendinous junction was also excised.

It was noted that the tissues offered some resistance to sectioning.

The pathology report was as follows: epidermis normal, collagen fibers normal, elastic fibers normal in number and size, subcutaneous tissue free of any infiltrate, epidermal appendages quite normal, no pathological change in muscle fibers.

Impression: Normal skin.

The postoperative course was uneventful. Healing appeared normal. The child was fitted with plaster splints about the knees so as to hold them in a partially flexed position. The tendency for genu recurvatum disappeared.

DISCUSSION

One should also bear in mind other disease conditions where hypotonia may be present. The most common congenital form noted in infants is amyotonia congenita or Oppenheim's disease. The deep reflexes are absent, the flail joints are due to muscular weakness, the reaction to faradic current is usually absent while that to galvanism is retained. Ehlers-Danlos disease should be considered with its increased elasticity of the skin, frequent subcutaneous hemorrhages following trauma, retarded healing of skin lesions, and hypermobility of the joints. There is a distinct difference in the histological picture from hypotonia.

Cerebellar disease usually shows other findings such as asynergia, tremor, and asthenia. Spinal cord

involvement in poliomyelitis and traumatic affairs where the anterior horn cells are concerned may show a flaccid condition. Patients with Marfan's syndrome, besides other characteristic findings, have a typical spider-like appearance of the extremities.

Deficiency diseases such as malnutrition, rickets, and hypothyroidism should be mentioned. Drugs such as intoxicants and sedatives are well known for their ability to produce hypotonia.

SUMMARY

A case report of hypotonia is presented with a review of the literature. The lack of muscular tone and hypermobility of the joints are the two outstanding features.

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DR. JOAQUÍN A. DE LA TORRE, COORDINATOR OF THE SESSION

Some Medicochirurgic Problems of Ascariasis

DR. J. A. DE LA TORRE (Head of Department in Medicine).—Three cases will be presented; with them we intend to illustrate some of the problems ascariasis produces in the child.

Dr. Díaz Herrera will outline briefly a few aspects of the biology and epidemiology of the parasite.

DR. ANTONIO DÍAZ HERRERA (Head of the Laboratory).—In Mexico City, ascariasis is endemic, and because of its frequency, it is the most important intestinal helminthiasis in childhood. In a study carried out by Dr. Luis Mazzotti,[1] parasitologist of the Instituto de Salubridad y Enfermedades Tropicales, in 36,545 stool samples from persons resident in this city, this was the nematode most frequently found, with an incidence of 7.8 per cent. In tropical zones of the country the incidence may be as high as 40 per cent.

Human infection is acquired through the ingestion of embryonated eggs which have been placed on the ground through defecations of individuals affected with the parasite. It is also acquired by the consumption of foods or drinks contaminated with human feces. Ascariasis is a disease acquired by children at home or on their playgrounds, when their hands, soiled with their own feces, are placed in the mouth.

This parasite does not require an intermediary host, but in order that infestation be produced, fertilized eggs must undergo, outside of the organism, a period of incubation which fluctuates between 30 and 45 days. This usually takes place in the earth. The eggs are quite resistant. Under bad climatologic conditions, they remain in latency for several months, but when there are favorable situations of dampness, shade, and a temperature between 22° to 33° C., the embryo is rapidly transformed into a first mobile larva stage within 9 to 13 days, passing later on to a second stage of larva of the same rhabditic type, and with a great infecting power. Under these conditions, if totally embryonated eggs are swallowed, they reach the duodenum where the action of the intestinal juices weakens the shell and stimulates the activity of the larva which emerges through a rupture, of a size 0.2 to 0.3 mm. in length by 13 to 15 μg in diameter. This larva pierces the wall of the small intestine and reaches the small mesenteric veins and lymphatic canals, whence, by way of the right circulation, it reaches the lungs. Here, after 10 to 11 days, after undergoing two mutations, the parasite erupts into the pulmonary alveoli, and later through the bronchioles, bronchi, and trachea, by way of the esophagus and

stomach, reaches the small intestine, where it develops into an adult worm capable of reproducing again.

In highly infected persons, larvae may pass from the alveoli to the capillaries of the pulmonary veins. In this manner, the left circulation is reached, and real parasitic emboli are produced. This explains the fact that parasites may be found in such organs as the thymus, spleen, thyroid, lymphatic glands, etc.

DR. DE LA TORRE.—Dr. Villalpando, who operated upon the first patient, will present the case.

Case 1. Intestinal Obstruction by Ascarides

DR. EDUARDO VILLALPANDO (Assistant Resident in Surgery).—L. O. I., a 9-year-old male patient, was admitted to the Hospital Infantil with a history of fever, abdominal pain, and marked toxicity for the last seventy-two hours.

The only important complementary history was that three days before hospitalization, and just preceding the appearance of painful phenomena, the patient expelled ascarides through the rectum.

Present illness was initiated abruptly three days before admittance, with vomiting of everything ingested or of yellowish mucoid material, with high fever, normal bowel movements at the onset, followed by constipation and, finally, bloody stools.

Physical examination: The child weighed 21.5 kilograms (first-degree malnutrition), was semistuporous, and there was poor response to stimuli. The oral temperature was 38° C., pulse rate 180 per minute, and arterial tension 95/60, pallor was present and the tongue and buccal mucosa were dry. The abdomen was distended, with muscular rigidity, tympanic sound on the upper half with dullness on the lower half and was painful on superficial palpation. Deep palpation was not possible. A digital examination revealed an empty rectal ampulla, hypotonic sphincter, and fetid dark red blood on the finger glove.

The blood picture was as follows: 4,800,000 red cells, with 11.6 per cent hemoglobin; 12,200 leukocytes, with 77 neutrophils, 20 lymphocytes, and 3 monocytes.

Plain x-ray of abdomen revealed opacity in lower half; there was no subdiaphragmatic air.

The tentative diagnosis was probable perforation by typhoid fever or volvulus.

Laparotomy was performed. About 250 c.c. of a yellowish-brown liquid was found in the abdomen. The small intestine, of a violaceous red color, was quite distended and edematous, and throughout masses of ascarides were felt, especially in two places of the ileum where the masses were so bulky that the lumen was completely obstructed. It was not possible to express those masses. Volvulus was also found.

Two ileostomies were performed in the places where larger accumulations of parasites were present. With the aid of ring forceps, 365 worms were removed and the obstructions disappeared, but a large number of parasites were still left within the intestine. The volvulus was corrected by rotating the intestine, which immediately improved its circulation and appearance.

The postoperative course was uneventful.

Other complementary tests, such as determination of plasma sodium and potassium, reactions of agglutination,

x-rays of the lungs, urinalysis, and repeated blood counts, were all negative. A stool examination showed eggs of ascarides (++++) and of trichuris (++).

Hetrazan was prescribed ten days after the operation, and a great number of ascarides were expelled during the following days.

The patient was discharged twenty-five days after admission.

the other two volvulus was also present. The ileum was obstructed in seven patients, and the jejunum in two.

In three patients with mechanical obstructions and the two with volvulus, the blood circulation of the intestine was so seriously affected that it was necessary to do resection and anastomosis, preceded by extraction of ascarides. The present case is the first

Fig. 1. Fig. 2.

Fig. 1.—Resected intestinal segment showing the length of the occluded portion.
Fig. 2.—Intestine with a large number of parasites.

DISCUSSION

Mechanical obstruction as a complication of ascariasis is frequent. Parasites tangle up in masses which may be found anywhere in the small intestine, and exceptionally in the large intestine. In addition to the present case, there have been eleven other children in the hospital in whom surgery also solved the problem. In nine the obstruction of the lumen was due exclusively to parasites, and in one with volvulus in which simple untwisting was followed by complete recovery. Volvulus is intimately related to the intense peristalsis caused by parasites, but in some cases it is important to take into account the abnormal mobility of the intestine or of its mesentery, and the weight of the parasites.

Three hundred sixty-five parasites removed are a considerable number. In another one of our cases there were 600.

The classical symptomatology consists of abdominal pain, vomiting, and constipation, together with a moveable mass, not painful, located in the umbilical region, and with a peculiar pasty sensation on palpation. This was found in six of our eleven cases. Possibly the signs of acute abdomen masked these findings in the rest.

Blood has been seen in the stools when there is a serious involvement of the intestinal wall; therefore, it may be considered as a sign of poor prognosis.

The expression of ascarides to the colon is not always easily accomplished, of which the present case is an example. It depends on the place where the obstruction is located, on the size of the segment obstructed, on the condition of the intestinal wall, and on the possibilities of forcing the parasites through the ileocecal valve. In some cases the disintegration of the mass of parasites and the consequent renewal of the free intestinal passage are sufficient to obtain the cure.

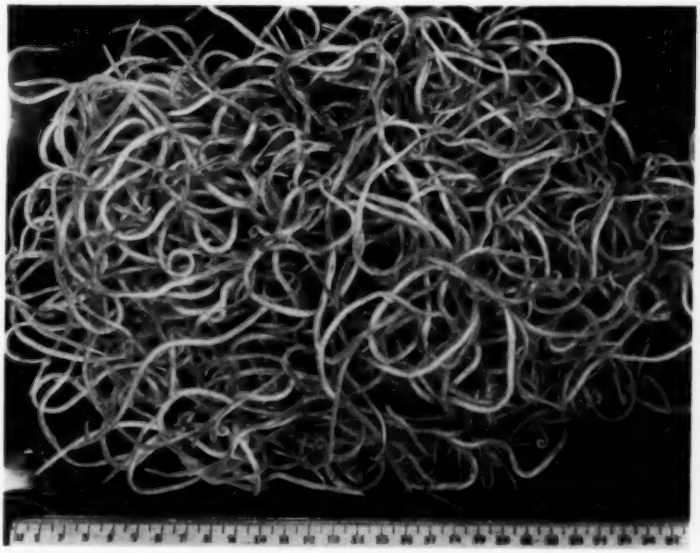

Fig. 3.—Skein of ascarides.

It is interesting to note the absence of eosinophilia. In our series, eosinophilia was present in only two instances.

In these cases the surgical technique has three aspects: (1) expression of ascarides from the small intestine to the large intestine through the ileocecal valve, (2) enterostomy with removal of parasites, and (3) intestinal resection.

As to enterostomy, the best procedure is to perform it in healthy tissue below the obstruction, in order to empty the septic contents of the loop and remove the parasites. Intestinal resections in our patients have always been followed by termino-terminal, or latero-lateral anastomosis. The outlook is always serious.

DR. DE LA TORRE.—In contrast with the mechanism of obstruction caused

by a large number of parasites, two other varieties have been described where the occlusive disorders depend on changes of tonus of the intestinal wall, caused directly by certain substances of the parasite. One is the occlusion by spasm, and the other by primary paralytic ileus. The rareness of these cases makes their evaluation difficult; the explanation of the mechanisms evoked is also doubtful. We have not found either of these varieties in our series.

We shall make some comments on the characteristics of the symptoms described by Dr. Villalpando. Pain, in plain intestinal occlusion, may have diverse modalities, from light, occasional painful crisis, to the violent, even syncopal, abrupt painful abdominal picture; usually, a gradual increase in intensity and frequency is observed until it becomes continuous. Nausea and vomiting are frequently early symptoms, and have diagnostic importance when ascarides are expelled. Although constipation is of capital importance, we had a patient in whom the stools were numerous, bloody, with mucus, and without fecal matter. The tumor mass, besides the characteristics already described, may at first be identified as small masses, in several places, which later gather into a single tumor.

Surgical ascariasis has a variable picture in which acute symptoms mask partially, or totally, those of ascariasis itself; thus, a diagnosis can only be established at the operation or autopsy. When the onset is acute, the clinician is inclined to think of appendicitis or intestinal obstruction of other nature, like intussusception. Frequently the only feasible diagnosis is that of acute abdomen, since there is no basis for a more concrete diagnosis. When the onset has been slower, and there have been prodromal stages, history of parasites, and painful and obstructive symptoms which have increased, the clinical elements at hand are sufficient to establish a well-founded suspicion. The presence of a tumor mass is a very important factor.

In our series of eleven patients, the youngest one died. Although the duration was only of two days, there were intestinal zones of necrosis.

Dr. Marcelino Figueroa (Resident in X-rays).—The images of ascarides in the intestine which we have in our files of radiology have been largely accidental findings when roentgen examinations of the intestine were made, or barium enemas were given for the examination of the colon. In children with intestinal occlusion by ascarides, the parasites have been observed in the small intestine with the use of suitable contrast media.

The images found are of two types. In one the parasite appears individualized by having ingested the barium meal and it has a filiform aspect. The other image is that of linear shadows with parallel striae caused by the barium adherent to the external surface of the worms. We have seen both varieties simultaneously in the same film. In other instances, even without means of contrast, there may be shadows suspicious of ascarides; this was the case of the third patient, which will be discussed in the conference. When the parasites are numerous, they resemble a skein with many helminths tangled up. If the obstruction is accompanied by peritoneal involvement, the intestinal coils may be seen distended, with thickening of the walls and fluid levels.

DR. DE LA TORRE.—Dr. Villalpando, we would like to learn some further details on anthelmintic treatment in these patients.

DR. VILLALPANDO.—In some cases an occlusive picture has been produced after the administration of purges or vermifuges, especially chenopodium. Even after operation, caution should be used in the administration of this type of medication. Diethylcarbamazine seems to have the advantage of not causing runaway movements of the parasites. In a series of twenty-five patients treated with doses of 10 mg. per kilogram of body weight t.i.d. for one week by mouth, we obtained, without resorting to purges, and without toxic effects, a total vermicidal action in 64 per cent of the cases.[2] In the conservative approach when only medical treatment is done, we advise the use of this product or else hexylresorcinol in small repeated doses without purgatives. We also recommend that antiparasitic treatment be withheld until ten days after operation.

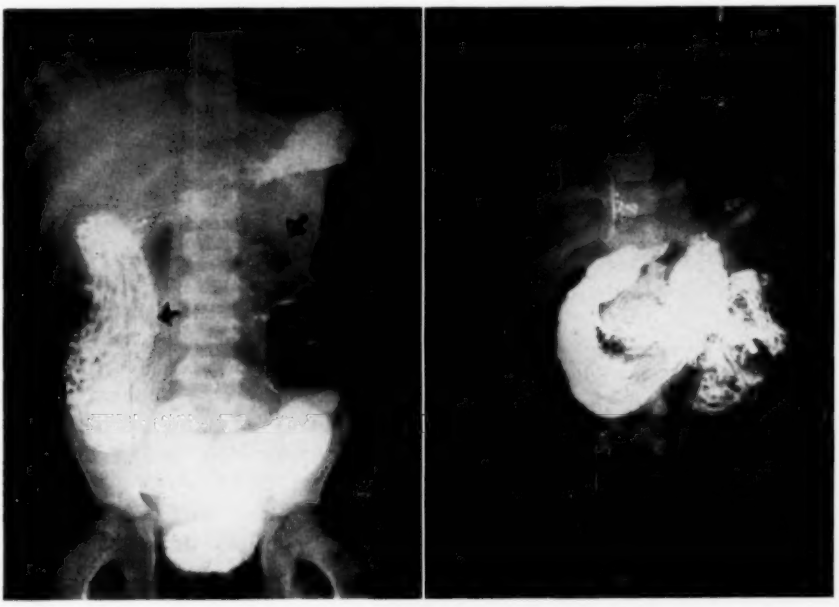

Fig. 4. Fig. 5.

Fig. 4.—Picture taken after barium enema; two groups of ascarides may be seen. No contrast was used for the group on the left side.

Fig. 5.—Aspect of ascarides after ingestion of the barium meal.

Case 2. Hepatic Ascariasis

DR. DE LA TORRE.—Dr. Barrera, who acted as surgeon for this second patient, will present the case and will make some comments on the problem.

DR. AGUSTÍN BARRERA (Assistant Resident in Surgery).—The case is that of a 5-year-old female who was referred from another institution with the diagnosis of hepatic abscess.

The chief complaints were an illness of two months with fever, and the presence of parasites in the stools.

Two months previously, the patient had colicky type abdominal pain. After the administration of purgatives, intestinal parasites were expelled on two occasions. One week later, an irregular fever began which was still present on admission. On several occasions ascarides were expelled through the rectum. One month after the onset frequent vomiting developed, composed of food rests and mucus, and abdominal distention without diarrhea. Taken to the health center "Dr. Antonio Márquez," a diagnosis of hepatic abscess was made. Pus was obtained at the liver puncture but its characteristics were not given.

Examination on admission revealed temperature, 37.5° C.; weight, 14.6 kilograms (second-degree malnutrition); pulse, 118 per minute; arterial pressure, 100/80. The patient was constantly complaining of pain; there was good orientation, and good response to stimuli, but with evidently bad general condition. There were subicteric tinge; moist, coated tongue; dental caries; slightly dull heart sounds, and a few coarse râles in both lung fields. The abdomen was distended and tympanic with percussible hepatic area. Liver edge was 6 cm. below the costal margin on the mammary line, and there were slight tenderness, abdominal rigidity, and pain on deep palpation.

The patient was admitted to the surgery department where an x-ray film of the abdomen was immediately taken. This showed dilatation of the ileum, and subdiaphragmatic air was suspected on the left side. Fluoroscopy revealed paresis of the diaphragm on the right side, and obliteration of the costodiaphragmatic sinus on the same side. The blood count prior to the operation was 3,250,000 red cells with 10 grams of hemoglobin, and 7,800 leukocytes with 41 lymphocytes, 59 neutrophils, 2 juveniles, and 3 staff cells. The search for amebae on the warm plate was negative.

That same day the patient was operated upon with the diagnosis of hepatic abscess. On opening the abdominal cavity, a collection of about 175 c.c. of light yellow color pus was found. The intestine was normal except for some fibrous exudates scattered along the surface. The liver appeared large, of a dark red color, and was covered with a coat of fibrin. A small abscess of about 2 cm. per side was found near the edge of the liver and at the level of the mammary line; it was punctured and a biopsy taken from it. Between the dome of the liver and the lower face of the diaphragm, which were closely adherent, another abscess was located. On incision, a large amount of pus of a bloody-yellowish color escaped. It was sutured, and drains left in place. After this, a right pleural effusion was punctured and about 8 c.c. of pus was obtained, which was similar in character to the pus of the subdiaphragmatic abscess.

In the pus from both the abscess and the effusion, *Escherichia coli* was isolated. This organism was susceptible to chloramphenicol and fairly so to chlorotetracycline and to oxytetracycline. Amebae were not found.

The postoperative period was uneventful; however, the fever persisted without change with daily peaks up to 39° or 40° C., alternating with normal or subnormal temperatures. This was the panorama of the fever for seventy-

seven days. The abdomen remained distended, painful, and draining pus in abundance.

During the first weeks it was necessary to give fluids intravenously. The solutions used were glucose and Hartmann's with potassium chloride; also hydrolytes of proteins, blood, and plasma. Penicillin, streptomycin, and sulfadiazine, which were given at the onset, were changed on the sixth day to oxytetracycline.

On the second day the blood count showed 4,080,000 red cells with 11 grams of hemoglobin, and 17,700 leukocytes with 65 per cent neutrophils. By the tenth day leukocytosis persisted with a figure of 15,300 of which 78 per cent were neutrophils. Alkali reserve twenty-four hours after operation showed 27 vol. of carbon dioxide. After sodium bicarbonate was given, it rose to 39 vol. At urinalysis, red and white cells were present +. Other tests, such as Mantoux, hemoculture, agglutination reaction, search for plasmodium and amebae, and stool culture, were negative. Direct bilirubin test gave 0.82 mg.; indirect, 0.70. Total proteins were 8.95 grams with 3.32 albumin, and 5.63 globulins, of which alpha was 1.59 grams., 1.07 beta, and 2.97 gamma. Thymol was 6 units, and flocculation ++. Cephalin cholesterol ++ in twenty-four hours, and +++ in forty-two hours. The x-ray film still showed elevation of the diaphragm on the right side, and atelectasis of the base on that same side.

The general condition remained unchanged, with a septic fever which was ushered by chills. There was dyspnea, and a few râles in lung fields. The treatment with oxytetracycline was changed after a week to chloramphenicol.

The biopsy of liver showed remains of *Ascaris lumbricoides* with areas of necrosis, and zones of infiltration by polymorphonuclear lymphocytes.

Considering the possibility of other hepatic abscesses, twenty-five days after hospitalization a second laparotomy was performed. A foul, purulent collection was found to have reaccumulated on the dome of the liver. By liver puncture, two more abscesses were located and excised; they were surrounded by sclerous tissue.

The culture of the pus obtained on this occasion was positive for *Esch. coli* with fair susceptibility to chloramphenicol, chlorotetracycline, and oxytetracycline. The blood culture was again negative. The blood count was 4,400,000 red cells with 13.4 grams of hemoglobin, and 24,000 leukocytes with 68 neutrophils.

There was practically no change in the general condition. The fever, abdominal distention, and abundant draining of pus continued. Six days after the second operation there were frank symptoms, which were verified at x-rays, of right pleural effusion. At the puncture, 100 c.c. of fetid, well-bound pus was drained; the culture for *Esch. coli* was positive. Chlorotetracycline administration was renewed.

As the right empyema recurred in spite of several punctures and the injection "in situ" of antibiotics, continuous drainage was substituted.

The white cell counts fluctuated between 29,000 and 8,000 with neutrophilia above 60 per cent. Repeated stool examinations showed eggs of trichuris exclusively. Thymol, cephalin cholesterol, and plasma proteins remained with the same variations mentioned in the first tests. The last bili-

rubin test showed 0.016 for the direct and 0.534 for the indirect. No other organisms were found at bacteriologic examinations. The last x-ray films showed only slight pleural thickening on the right side.

The temperature finally became normal seventy-eight days after hospitalization. The general condition improved and the patient was discharged 117 days after admission.

DISCUSSION

At the onset, the interpretation of the entire picture through a single etiological cause seemed difficult, although there were grounds to suspect especially amebic hepatic abscess. Such possibility could not be totally discarded by the lack of identification of amebae in the stools, nor by the absence of a history of diarrhea.

The pathologic study revealed hepatic ascariasis. We consider the peritonitis secondary to the same process.

Ascariasis of bile ducts and liver is relatively rare. Ascariasis of bile ducts produces lesion by mechanical obstruction, and an associated infection. If the obstruction is not removed, the infection ascends and produces small abscesses which may vary in size from one to several millimeters. In other cases, as the present, the parasite invades directly the liver parenchyma and gives origin to larger abscesses.

Unfavorable intestinal conditions for the life of ascarides have been invoked as causes to explain their emigration to the pancreas, liver, and stomach, or through the intestinal wall to the peritoneum. Probably the use of purgatives in this patient caused the parasite to flee.

Liver puncture, as a diagnostic means, should be considered as a delicate procedure to be used only under exceptional conditions.

DR. DE LA TORRE.—Would Dr. Torres de Anda wish to say a few words on the problem of empyema?

DR. A. TORRES DE ANDA (Consultant in Chest Surgery).—For the first weeks the disease was chiefly located in the abdominal cavity, and it was only after the second operation that pleural manifestations became an important part of the clinical picture. Although the effusion was not considerable, repeated punctures and the local application of antibiotics were of little benefit. In empyema, subsequent to hepatic abscess, the mortality rate is high. In localized empyema, the surgical conduct advisable is the so-called "open drainage." In the present case the Waterseal procedure was used, producing a rapid decrease of the secretion and a full lung expansion.

DR. DE LA TORRE.—Dr. Salas will outline the conclusions of the Pathology Department in this case.

DR. MAXIMILIANO SALAS (Head of the Pathology Department).—During the migration stage of ascarides within the human organism, the parasite may not enter the lesser circulation, but skips the "pulmonary filter" to alter, in this manner, its biologic cycle. Through the systemic circulation, it may then stop ectopically and develop in any organ of the body. In such cases the presence of larvae, deeply seated within the tissues, gives origin to hemorrhages, necroses, or abscesses, without the parasite reaching its adult stage. In other instances the larvae enter the pulmonary circulation and

respiratory organs, and return again to the intestine, whence they may ascend through the bile or pancreatic ducts where they attain their full development. Due to the gradual growth of the parasite, the ducts, where it is lodged, become slowly dilated with consequent atrophy of the epithelium, and pericanalicular fibrosis. Due chiefly to associated bacterial infections, abscesses may occasionally be formed.

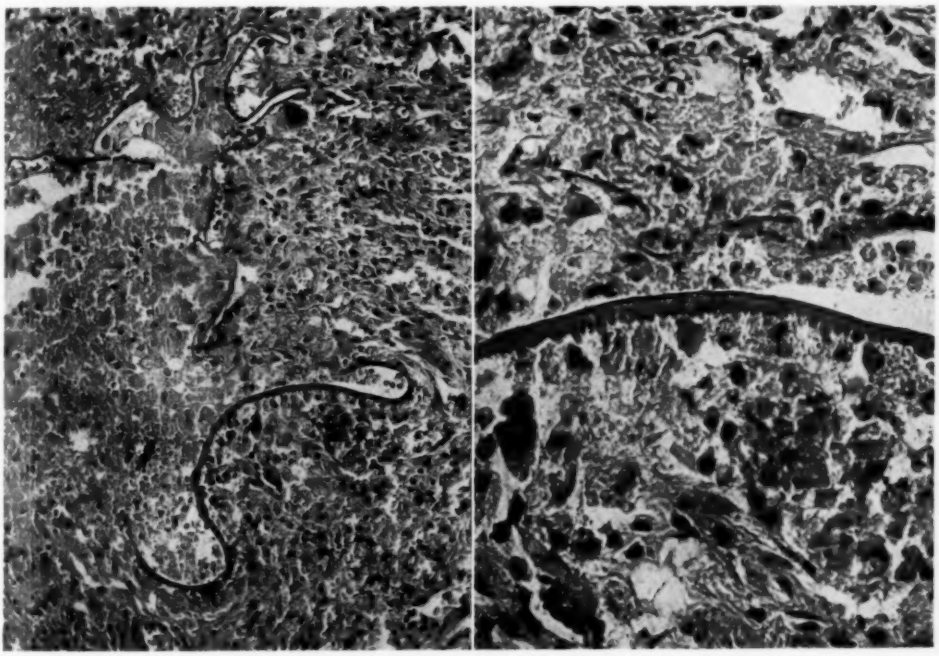

Fig. 6. Fig. 7.

Fig. 6.—Photomicrograph showing ascaris remains within an area of necrosis with inflammatory reaction and fibrosis. Low-power enlargement.

Fig. 7.—Photomicrograph seen at higher power to show some details of the wall that limits the body of the parasite. High-power enlargement.

In this particular case it was possible to establish a diagnosis of hepatic ascariasis because of the identification of adult parasite remains within the parenchyma. Following the general ideas in this respect, it is very likely that the larvae climbed the bile ducts where they finished their growth. The dead parasites, plus the probable aggregate of the bacterial association, produced the inflammatory reaction found at biopsy.

DR. DE LA TORRE.—This is the second case of hepatic ascariasis we have seen in the hospital. In the other patient, who only lived a few hours after admission, the clinical diagnoses of hepatic abscess and empyema were made. At autopsy, empyema was confirmed and hepatic ascariasis was discovered.

Although the clinical picture of ascariasis of the bile ducts in the child

may follow the same pattern as in adults, that is, with symptoms of mechanical jaundice, or cholecystitis, angiocholitis, or cholelithiasis, of more or less slow evolution, usually such data do not exist or are masked by those of helminthiasis, or by the serious symptomatology of hepatic abscess. In that case there is a febrile picture with great oscillations in temperature, attack to the general state, and local symptoms.

The important clinical differences between these two varieties seem to depend chiefly on whether or not there is an added infection, which is practically inevitable when the disease deals not with larvae (as in granuloma of the liver), but with adult parasites.

The third case illustrates another variety of complication of ascariasis. It is the only instance of probable intestinal perforation by ascarides we have on record at the hospital. Dr.

Fig. 8.—Ascarides within hepatic parenchyma.

In contrast with our observations, in medical literature from the United States there have appeared reports[3] in children with febrile pictures, hepatomegaly, and eosinophilia, in whom the final prognosis is good. Larvae of ascarides were demonstrated at biopsy of the liver.

Sariñana will present the case history, and make a few comments on it.

Case 3. Intestinal Perforation by Ascarides

Dr. Carlos Sariñana (Resident in Surgery).—H. C. V. A., a 6-year-old female, was admitted with a history of an eight-day illness with vomiting,

tympanites, and abdominal pain. There had also been deficient feeding.

The present illness had its onset ten days ago, being initiated by diarrhea, in which there were four movements a day, watery, yellowish, and foul, but without mucus or blood. Two days later, intensive colicky pain developed which was referred by the patient to hypogastrium and hypochondrium. There was mucous vomiting, yellowish, and with food rests. Since then, there have been fever, anorexia, and, in the last five days, constipation.

Physical examination revealed a female of preschool age, weight 15 kilograms (second-degree malnutrition); pulse, 120 per minute; temperature, 38° C.; arterial pressure, 77/40.

Examination further revealed dry tongue, sunken eyes, poor response to stimuli, very distended and tympanic abdomen, prominent collateral circulation, spontaneous pain; on superficial palpation, there were muscular resistance which impeded deep palpation, nonpercussible hepatic area, nonpalpable spleen.

The digital examination of the rectal ampulla showed it was full of fecal matter; also contractured sphincter. Traces of mucus and blood remained on the examining finger glove.

The white count showed 19,720 leukocytes with 90 neutrophils, 8 per cent lymphocytes, and 2 per cent eosinophils. There were negative reactions of agglutination.

The x-rays did not show perforations of intestinal coils; these were grossly dilated with thickening of the walls. The lateral film revealed a shadow which was interpreted as a probable ascaris.

A few moments after the film was taken the patient expelled an ascaris through the rectum.

The patient was operated upon with the diagnosis of acute abdomen and generalized peritonitis, consequent to probable perforation by ascarides. On entering the abdominal cavity, the intestinal loops were found distended and adherent to each other. There were abundant, fetid, creamy pus and a free ascaris in the cavity. In the terminal ileum, at approximately 10 cm. from the ileocecal valve, a round perforation of about 2 mm. with smooth borders was found. No areas of intestinal occlusion by ascarides were seen. The perforation was sutured, and drains were left in the peritoneal cavity.

The postoperative course was stormy, and was characterized by intermittent high fever until the moment of death. Constipation was present for the first four days, after which the bowel movements became gradually more frequent until the last days when a frank diarrheal picture, with nine to ten stools containing mucus and blood, complicated the process. In addition there were occasional vomiting of food, stupor, and dehydration.

Reactions of agglutination were negative for salmonella. *Esch. coli* was cultured from peritoneal pus. A second blood count showed 6,000,000 red cells, with 16 grams of hemoglobin, and 18,300 leukocytes with 90 neutrophils. The chest plate showed slight hilar reinforcement.

This picture, serious in itself, was complicated by a fecal fistula. The patient was again operated upon seventeen days after the first interven-

tion. A purulent fluid was found in the peritoneum, with many adhesions of intestinal coils, and lack of coalescence of intestinal sutures. In spite of adequate use of antibiotics and nursing care, the patient became worse, and died twenty-one days after hospitalization. Post-mortem study was not granted.

DISCUSSION

Perforations by ascarides have been classified into primary, which are those where the parasite bores through a healthy intestinal wall, and secondary, where there is an associated disease, such as typhoid fever, intestinal tuberculosis, etc., which would favor perforation. In this same group are classed intestinal perforations subsequent to surgical intervention, where parasites squeeze through the sutures. In our patient we found an intestinal perforation with smooth borders 2 mm. in diameter, about 10 cm. from the ileocecal valve. Although no autopsy was performed, which would be the only conclusive means of assuring an ascaridial etiology, this diagnosis was suggestive. In our experience, the most frequent association in intestinal perforation is that of ascariasis and typhoid fever. In thirty-five cases of intestinal perforation by typhoid fever studied by Dr. Navarro Franco and myself,[4] we found nineteen (54.12 per cent) where there was a parasitosis added. This high percentage of parasitosis in perforation could indicate a certain etiological relation between the two factors.

It was not possible to prove typhoid fever in this patient, and its existence seems doubtful because of the findings at operation. When typhoid fever is the cause of perforation, the pattern is like a hollow punch surrounded by a reddened zone and edema, and marked congestion of Peyer's patches. None of these were present in our case; the perforation was a single one with smooth borders.

We have no case on record where a perforation took place before the tenth day of illness, as it apparently happened in this patient.

DR. DE LA TORRE.—Intestinal perforation in the course of ascariasis may be considered as a rare feature, so much so that not all authors agree on the possibility of active perforation of the intestinal wall by the parasite. Those who deny such possibility base their argument on the weak traumatic power of the parasite and contend that the elastic layer of the wall would frustrate any action of this type. They also contend that perforations are post mortem, or else due to some other independent mechanism.

The most generally accepted opinion is that there are indubitable cases of intestinal perforations due directly to ascarides. In 1902, Solieri[5] collected the reports of twenty-one patients with perforations of the small intestine by the helminth; in six the perforation was in the stomach, in two in the appendix, and in one in the cecum.

Once the possibility of intestinal perforation has been admitted, it has been assumed that ascarides secrete certain substances capable of producing circumscribed inflammation and necrosis which, associated with the traumatic action of the parasite and with a secondary infection by pathogenic germs, would produce zones of lesser resistance.

These three cases illustrate the potential danger of ascariasis, and help the pediatrician and the surgeon to keep in mind their possibility when establishing a differential diagnosis in cases of acute abdomen in children.

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IN 1944, Kanner[1] described a clinical syndrome in children to which he gave the name "early infantile autism." Though great variations were observed in the severity of the disturbance, in the way specific features manifested themselves, and in the progression of symptoms, yet certain common characteristics were present to the extent that the condition may be considered a clinical entity. Kanner's delineation of this syndrome marks one of the notable advances in clinical child psychiatry.

SYMPTOMATOLOGY

The most striking symptom and, at the same time, the one which is common to all children with this disease is an inability to relate in the ordinary way to people and to situations. The children seem self-sufficient and want to be left alone. People, even their own parents, appear to have no meaning for them. They seem uninterested in the conversation going on about them and, when addressed, answer not at all or perfunctorily. They pay no attention to comings and goings. Unlike the ordinary child who, when tired or unhappy, reaches for a parent, the autistic child remains apart.

The desire to be alone is already evident in early life. As infants they seem unusually apathetic. Their indifference to people may lead to a suspicion of deafness. They withdraw from anything that disturbs their isolation—persons, noises, moving objects, and often even food. They fail to assume the usual anticipatory posture to being picked up, a form of behavior which is present in normal infants by 4 months (Gesell). Moreover, when they are picked up they do not adjust their posture to the person who holds them. Kanner states that at no period in the child's development has adjustment been normal.

Whereas the autistic child relates poorly to persons, usually completely disregarding even his parents, he relates well to objects. He seems interested in them and can play happily for hours. He can be affectionate with them or angry with them.

A second symptom regularly observed in the autistic child is a failure to use language properly. The following abnormalities in speech are observed:

Mutism: A considerable proportion of patients remain mute for several years after speech is normally acquired. However, this is not true muteness since at least some of the patients can speak and, in emergency situations, they may use single words or well-formed sentences. Even after speech is acquired, autistic children do not seem to enjoy this activity and speak little.

Parrotlike repetitious speech: When sentences are finally formed they remain for a long time merely parrot-

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like repetitions of word combinations previously heard. Sometimes the sentences are echoed immediately; at other times they are retained by the child and uttered at a later time (delayed echolalia).

Difficulties in using "yes": Infantile autism is ordinarily recognized at an age when normal children find it easier to say "no" than "yes." Such behavior is exaggerated in the afflicted child. He is generally unable to use "yes" to indicate assent and often indicates affirmation by literal repetition of the question.

Confusion in the use of personal pronouns (mixing up "you" and "I" and so on) is commonly observed in young children but the confusion is more marked in the autistic child and persists until a later age.

The third prominent symptom of infantile autism is an intense desire to maintain the sameness of the environment. The child actively resists changes of routine, of furniture arrangement, of toy arrangement, and so on, and goes into a panic until the previous order is restored. Minor changes in the environment which would ordinarily go unnoticed by the average child may elicit extreme anxiety in the autistic child.

Intelligence: Because of their failure to use language normally and because of their bizarre behavior most autistic children are, at one time or another, considered feeble-minded. This is, however, a false impression. Autistic children have intelligent physiognomies and give an impression of serious-mindedness. Some of the speaking children have astonishing memories and can repeat verses or prose pieces, even in foreign languages which they do not understand.

Kanner makes no mention in his cases of the phenomenon of unusual sensitivity to sensory stimuli which was described by Bergman and Escalona.[2] These severely disturbed infants, who later on turned out to be psychotic, reacted excessively to various stimuli—sound, touch, temperature, equilibrium, color, taste, smell, and so on.

CASE REPORT

Early Infantile Autism in One-Egg Twins

The twin boys, 23 months old, were brought to the Center because they did not yet speak and because they did not play together or with strange children. They completely ignored their parents or other persons and fought with each other on slight provocation. At times one or the other twin would go around in a circle and this would continue until he was stopped. Though ordinarily uninterested in toys they sometimes played with a single toy for hours. When taken from their nursery and placed out of doors they screamed until they were put back inside. They enjoyed horseplay.

Their peculiar behavior was first observed when they were about one year old but even before this the parents remarked that they were never affectionate children.

There was no history or mental disease in the parents or near relatives. Neither the parents not the grandparents were related. The father was employed as a salesman in a retail establishment. The parents showed a warm interest in the children. An older child, a girl, 5½ years old, was normal. The mother had a miscarriage between her birth and that of the twins.

Uniovularity of the twins was established by the presence of a single placenta at birth, the striking similarity in the facies and in the skin, hair, and

eye color, and the identical results in a battery of blood group tests.*

The mother was very much disturbed emotionally during pregnancy. She "spotted" repeatedly. Her appetite was finicky but she ate a general diet. Fetal activity was normal. There were no febrile episodes.

The children were born at term and weighed 2.3 and 2.4 kilograms, respectively. According to the obstetrician only one placenta was present. Birth and postnatal course were uneventful.

On examination the children were indistinguishable in size and appearance. Skin color and hair color were identical. Heights and weights were within the normal range. Muscle development, skin turgor and color were good. Muscular coordination was good. They not only did not speak, they made very few sounds except for crying. They stood, staring off into space as though absorbed in thought, making bizarre movements with the hands and fingers, showing no awareness of the persons about them and only occasional slight awareness of each other (Fig. 1). At times a smile appeared on their faces. When disturbed they resisted and cried, then lapsed back into their seemingly thoughtful state. Skull x-rays and electroencephalograms were normal.

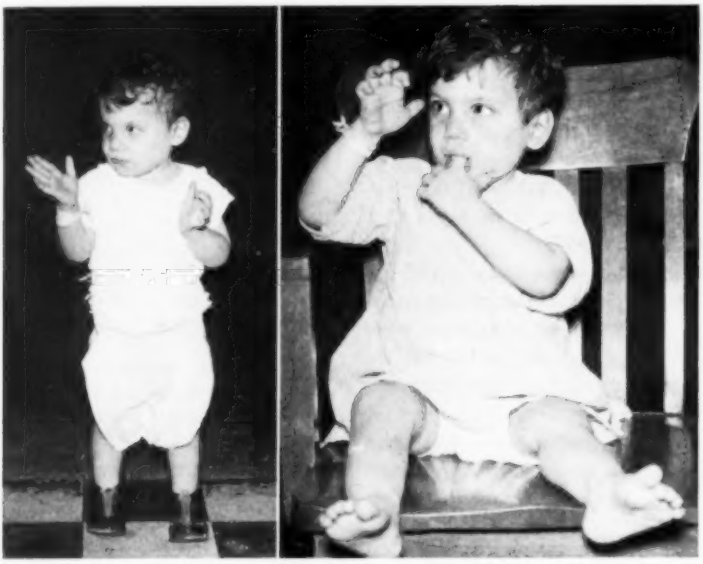

Fig. 1.—One-egg twins, 23 months old, with early infantile autism.

They had pneumonia at 6 weeks and received oxygen for a week. At 6 months they had asthma and received oxygen again. One of them had an operation for inguinal hernia at 6 months. Recovery was uneventful. Motor development was normal. Toilet training was unsuccessful. The children were thumb-suckers and bedrockers. They had certain eating peculiarities. They would not eat sweets. Since they did not hold anything in their hands they had to be fed. One of them was a slow chewer.

*Blood group testing was done in the laboratory of Dr. F. J. Kallmann.

DIAGNOSIS

Infantile autism presents a well-defined clinical picture which the physician accustomed to seeing children should be able to recognize readily. The outstanding clinical features are

the failure to show interest in the parents or other persons; the abnormalities in speech development (mutism, scant speech, echolalia, difficulties with the use of tenses and pronouns), and, at the same time, a history of normal motor development; and the intense desire for maintaining the same environment, the child reacting to change with extreme anxiety.

The following conditions are to be considered in the differential diagnosis:

Mental retardation: The delay in speech development often leads to a diagnosis of feeble-mindedness. This can be ruled out by the history of normal motor development and by the facial expressions which are intelligent and thoughtful. Though the usual Binet-Simon type of test cannot be used, performance on the Sequin form board is good. Moreover some of the speaking children have astounding vocabularies and excellent memories for tunes, poems, names, dates, and so on.

Deafness: The failure to respond to commands and the seeming unawareness by the patients of persons sometimes suggest a diagnosis of deafness. This can ordinarily be readily ruled out by a careful history and by observing the reaction of the child to the usual hearing tests with bells, whistles, and so on. Children who are able to hum familiar tunes obviously have some hearing.

Word deafness or, more properly, verbal-auditory agnosia,[3] which is characterized by inability or difficulty in recognizing the spoken word, must be considered in some cases. Children with this rare abnormality respond to ordinary sounds normally. Here, as in infantile autism, the children are mute or talk sparingly. They do not, however, show the difficulties in relating to persons and the obsessive desire for sameness of environment characteristic of the autistic child.

Developmental retardation of speech: By far the most frequent cause of late development of speech is a developmental abnormality in the areas of the brain which governs the language functions. Some children with this abnormality do not begin to talk until they are 3½ years old. When speech finally begins it is usually at first unintelligible or difficultly intelligible. The mature speech may be pure, cluttering, or impure. Children with developmental retardation in speech may be differentiated from autistic children by the absence of the behavioral manifestations characteristic of the latter condition.

Heller's disease is an acute degenerative disease of early childhood. It begins more or less abruptly at 1½ to 4 years of age, following a period of normal mental development. The characteristic symptom is a progressive deterioration of all aspects of mental functioning to the point of idiocy. Morphologic changes in the brain are present. The important differential features, according to Kanner, are the abruptness of the onset and the appearance of feeling and being sick which characterize children with Heller's disease.

Schizophrenia: Kanner[4] regards infantile autism as the earliest manifestation of schizophrenia. The basic nature of the manifestations of infantile autism is so intimately related to that of childhood schizophrenia as to be indistinguishable from it. Infantile autism presents a clinical picture of its

own and deserves a separate place because of the early age at which the symptoms appear.

ETIOLOGY

It is Kanner's view that the personalities, attitudes, and behavior of the parents of autistic children contribute to the psychodynamics of the patients' abnormal condition in the same way as emotional deprivation in early childhood alters the personality in later life.[5] The parents, with few exceptions, are cold, obsessive, and mechanical in their attitude toward the child. They lack warmth and genuine interest and regard the child as a subject for observation and experimentation.

A large proportion of the fathers are successful professional and businessmen. They are for the most part scientists, college professors, artists, clergymen, business executives, and the like. The mothers, with few exceptions, have attended college and have been active before marriage, and some also after marriage, as scientists, laboratory technicians, nurses, physicians, librarians, artists.

Aside from their high intelligence, the parents are generally of the type that is uncomfortable in the company of people, preferring reading, writing, painting, making music or just "thinking." They are, on the whole, serious minded and disdainful of lighter things.

Matrimonial life is cold and formal. There seems to be no close bond of affection between the parents; on the other hand there are no major animosities. In Kanner's series of fifty-five cases only one separation or divorce had taken place.

A prominent feature in the family histories is the absence of overtly psychotic or hospitalized members in the ancestral backgrounds of the children. The family trees of fifty-five patients failed to elicit a history of psychosis or committable mental disorder in the relatives. With the exception of the paternal aunt of one child, no instance of schizophrenia, manic-depressive psychosis, or even senile psychosis was found in the parents, grandparents, uncles, or aunts.

Infantile autism, as an early-appearing reaction to the type of parents just described, fails to explain the facts that (1) the siblings of autistic children are generally normal (it being rare to have more than one case in a family), and (2) infantile autism is sometimes seen where the parents are normally warm and affectionate. Kanner and Eisenberg[8] incline to the view that the disorder stems from an innate disability to relate to people, which is further influenced adversely by the personality deviations of the parents and their attitudes toward the child. Another consideration may be the confused reaction of the parents to the strangely behaving child. According to Kallmann[6] the predisposition to schizophrenia depends on the presence of a specific genetic factor which is probably recessive and autosomal.

Sex: Infantile autism is much more frequent in boys than in girls. Of the twenty cases reported by Kanner in 1944,[1] sixteen were boys and four were girls. Schizophrenia in later childhood shows a similar sex distribution. In a series of 626 children under 14 years of age, diagnosed as having schizophrenia, Bender[7] found the ratio of boys to girls to be 2.66.

PATHOLOGY

There are no reports of examination of the brains of children with infantile autism.

PROGNOSIS

The outlook for children with early infantile autism is the subject of a recent communication by Kanner and Eisenberg.[8] They were able to follow forty-two patients from four to nineteen years after the first acquaintance (average, eight and one-half years). The age range of the patients at the time of inquiry was 8 to 24 years (average, 14 years).

The prominence of speech disturbances in the early years was found to have useful prognostic implications. Of the nineteen children who did not talk at around 4 years of age, eighteen were still enveloped in their shells and impressed the observers as feebleminded. Seven of these were in institutes for mental defectives, seven others were at home in a well-nigh helpless state, two were on farms, and two were in state hospitals for the insane. Only one of the nineteen children, a boy of 11 years, was able to function at school acceptably.

The picture presented by the twenty-three speaking children was somewhat less disheartening. Ten of them did poorly: of these, five were chronic state hospital patients, three were in schools for retarded children, one was on a farm, and one was at home. Most of them, however, still retained remnants of mental functioning which would distinguish them from the demented or pseudodemented level of the mute autistic group. None of the patients displayed delusions or definitely ascertainable hallucinations.

The remaining thirteen members of the speaking autistic group were able to function with some degree of competence at home and in the community. One had served in the Navy as a meteorologist, was married, and had attained some eminence as a composer. The other twelve attended school and performed acceptably there. Their personality is described by Kanner and Eisenberg as "markedly schizoid. . . . For the time being, they maintain a tenuous contact with reality."

TREATMENT

Kanner and Eisenberg[8] state that none of the varieties of psychiatric treatment employed had any noticeable effect on the course of illness of their patients. It seems wise to surround the child with warm, affectionate, demonstrative adults.

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Comments on Current Literature

HIRSCHSPRUNG'S DISEASE IN THE NEWBORN INFANT

THE July, 1954, issue of the *American Journal of Surgery* carries an article in which Russell R. Klein and Robert A. Scarborough[1] point out that the most frequent indication for surgery in the newborn infant is intestinal obstruction, and that in addition to the well-known causes for this condition, consideration must be given to possible neurogenic obstruction of the distal colon, or Hirschsprung's disease. In a survey of the literature these authors found recorded approximately fifty cases of Hirschsprung's disease in infants with a mortality rate of 70 per cent. In their own series of five infants, there were three deaths or a 60 per cent mortality.

Since it is agreed that symptoms associated with Hirschsprung's disease may date from birth, the recognition and management of this disease in the newborn period are of considerable importance. The authors are in agreement with the impression generally held that localized absence of ganglionic cells in the myenteric plexus of the rectum and sigmoid colon is the underlying cause, such absence of ganglionic cells allowing functional partial obstruction of the intestine to occur which is associated with secondary dilatation and hypertrophy in the bowel proximal to this area.

The authors are well aware of the difficulties encountered in making the diagnosis during the newborn period, and emphasize that final proof can be established only on demonstration of the absence of ganglion cells in the rectum and distal colon. In all of the five infants included in their present report, the general appearance at birth was normal with no external evidence of congenital anomalies. Regurgitation was noted on the first or second day of life; material regurgitated was usually bile stained. In each of the five infants vomiting was a prominent feature of the difficulties of early life, and persisted despite attempts at medical management. Soon after the onset of vomiting abdominal distention was noted. While meconium was passed in small amounts, and in some instances small stools followed the meconium, in no case was bowel function considered normal. Improvement brought about by means of enemas and other palliative measures was temporary. In two of the five infants, definite narrowing of the lower portion of the rectum was evident on digital examination.

In each of these newborn infants the clinical picture was suggestive of intestinal obstruction, and x-ray studies were undertaken in an attempt to detect the level of obstruction and, if possible, ascertain the underlying cause. The authors summarize the typical x-ray findings of Hirschsprung's disease in the newborn infant as follows:

> "(1) Dilatation of both large and small intestine on the plain film, with no air in the rectal ampulla; (2) disparity in diameter between the dilated colon and the non-dilated rectum; and (3) evidence of a poor power of evacuation as shown on the twenty-four-hour postevacuation film."

Once the diagnosis of Hirschsprung's disease is suspected in the newborn baby, approach to management is the point at issue. The authors emphasize that the object of therapy is the correction of the functional obstruction at the distal end of the colon and rectum. In some instances, correction may be accomplished by conservative measures such as administration of saline enemas, or

the use of a soft catheter inserted through the rectum beyond the segment of dysfunction, with effective irrigation through the catheter. These authors feel, however, that in each individual case surgical decompression of the bowel proximal to the obstruction must be considered seriously. In their opinion, if conservative management in these newborn infants does not relieve the obstruction and establish normal digestive tract function within one week, surgical intervention is indicated, colostomy being the procedure of choice in their experience. According to Klein and Scarborough, resection of the aganglionic segment should be postponed if at all possible until the second or third year of life.

In keeping with recommendations made by authorities in this field, the authors suggested that a biopsy of the bowel be taken at the site of the colostomy in order to demonstrate the presence of normal ganglia, and that muscle biopsy studies of the wall of the rectum and the sigmoid colon should be made in order to be certain of the diagnosis of Hirschsprung's disease.

While this particular series of cases is small and the final results not too encouraging, the report is of considerable interest to physicians faced with the care of newborn infants who are not doing well. Since at best, the causes of neonatal obstruction are difficult to differentiate clinically, and since mortality has been high in newborn infants with Hirschsprung's disease in whom the condition was not recognized early, it appears reasonable, as these authors point out, that Hirschsprung's disease should be considered whenever obstruction is seen in the newborn infant, especially in those instances where, despite all efforts, no definite anatomic cause can be made apparent. With early diagnosis and close cooperation in medical and surgical management, perhaps this important congenital malformation can be corrected at an earlier time in the patient's life than has been possible heretofore.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

In a letter to the Editor, in the July, 1954, issue of THE JOURNAL OF PEDIATRICS, Dr. Henry H. Beinfield states his belief that bilateral congenital choanal atresia may be responsible for many asphyxial deaths in the newborn period, that the condition has been generally forgotten since the work of Otto in 1829, and that the pathologist in performing an autopsy on an infant dead of asphyxia usually overlooks the examination of the posterior nares either because of ignorance or to avoid "mutilation of the body before burial."

It is quite true that the subject has been referred to mainly by the otolaryngoscopist or the radiologist. References to congenital choanal atresia in pediatric literature are few in number. Only 115 cases of bilateral atresia are recorded in the literature up to 1945. Five cases, three of them bilateral, were seen within a two-year period by the writer and reported in the pediatric literature (Medovy, Harry, and Beckman, I. H.: Pediatrics 3: 678, 1951). In this report it is stated "Congenital occlusion of the posterior nares is a rare cause of asphyxial attacks in the newborn infant. . . . It is important also for the pathologist to keep this condition in mind when doing an autopsy on an infant dead of asphyxia. It is quite possible that in many instances the examination of the nares is overlooked in death, as it is in life, and that some infant deaths . . . may in fact have been due to asphyxia resulting from an occluded nasal airway."

In the three years which have elapsed since the above article was submitted for publication, careful examination of the posterior nares has been performed in all cases of asphyxia, mild or severe, in a large maternity service (3,000+ deliveries per annum) and by the pathologist in all neonatal autopsies. No further cases have been encountered. Similar passage of a metal sound by the pathologist is sufficient to demonstrate the presence or absence of this malformation. No mutilation is necessary.

Congenital bilateral choanal atresia is an *important* but *rare* congenital malformation. No autopsy on a case of asphyxial death in an infant should be considered complete until the nasal openings are examined.

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News and Notes

At the annual meeting of the **Section on Pediatrics of the A. M. A.** at San Francisco on June 24, the following officers were elected for the ensuing year:

Chairman: Dr. William Weston, Jr., Columbia, S. C.
Vice Chairman: Dr. Thurman B. Givan, Brooklyn.
Secretary: Dr. Wyman C. C. Cole, Detroit.

Dr. W. L. Crawford, Rockford, Ill., was continued Section delegate, Dr. F. T. Mitchel, Memphis, representative to scientific exhibit, and Dr. Hugh L. Dwyer, Kansas City, custodian of the Jacobi Fund.

On September 23 to 25 the Department of Pediatrics of the **University of Minnesota** in conjunction with the **Northwestern Pediatric Society** held a "Grand Reunion" in honor of Dr. Irvine McQuarrie who has been head of the department for twenty-five years. There was an extensive program in which twenty-two speakers from many parts of the country took part, including many of Dr. McQuarrie's former assistants who are now teaching in other medical schools. A "McQuarrie Pediatric Fund" has been established to provide income for various pediatric activities of the department.

Book Reviews

Child Health and the State. Alan Moncrieff, C.B.E., M.D., F.R.C.P., 1953, Oxford University Press, 48 pages. Price $1.50.

A small volume containing the three Newsholme lectures delivered last year by Dr. Moncrieff, Professor of Child Health of the University of London. The titles of the lectures were "Infant Welfare," "School Health," and "The Deprived Child." The author discusses the successes, failures, and shortcomings of the assumption of responsibility for child health and welfare by the state. The fault or danger, as Moncrieff sees it, of the "welfare state" lies in its weakening or lessening the obligations of parental responsibility. "The general attitude is unfortunately that of *taking* out of the national pool and putting nothing back. There is a willingness to accept all that the State offers without a corresponding readiness to make a contribution in return." The three lectures reflect the calm thinking of one who has been intimately connected with the working out of the welfare state in its application to children. It is neither propaganda for nor an attack on the assumption of responsibility by the state. As he puts it, the welfare state means "the sacrifice of one freedom in order to gain another—freedom from want."

Emergency Treatment and Management. Thos. Flint, Jr., M.D., Philadelphia, 1954, W. B. Saunders Company, 303 pages. Price $5.75.

This is an unusually useful and practical book by the chief of the Emergency Department of the Kaiser Foundation Hospital in California. It covers about every emergency condition which must be treated instantly by the physician or in the hospital receiving room. The emergencies are arranged alphabetically, which should prove of help for quick reference when needed. Thus, the first subject is "abdominal pain" and the second, "abortions." The section on "poisons" is unusually complete, covering about a third of the text. Here, again, the various poisons are listed alphabetically—acetanilid, acetic acid, acetone, and so on to Zygadenus. Each covers the symptoms and treatment. This section ends with a list of the poisonous ingredients in several hundred commercial preparations, such as weed killers and rat poisons, which are sold without restriction and often without sufficient label. It should prove a very useful book for hospital admitting rooms.

Lehrbuch der Paediatrie, ed. 3. G. Fanconi and A. Wallgren, Basel, 1954, Benno Schwabe & Co., 965 pages. Price $18.00. (Intercontinental Medical Book Corporation, 381 4th Ave., New York 16.)

A third edition of Fanconi and Wallgren's textbook of pediatrics which was first published as recently as 1950. It has received an excellent reception in European countries. The first edition was translated into English and has previously been reviewed in the JOURNAL. The second edition was translated into Spanish and Serbo-Croatian, and this third edition is being translated into Yugoslavian. The text has a definite international character as nineteen well-known pediatricians from Switzerland, Norway, Sweden, Holland, Germany, Ireland, Finland, and Turkey have contributed sections. Many new illustrations appear in the third edition, and the various chapters have been revised to keep pace with pediatric progress. It is essentially a textbook rather than a book of reference, as throughout the text, references, and even names to a large extent, are not included. The reviewer, in reading a number of sections, has found the description of disease clear and concise and the therapeutics practical.

Editor's Column

IS BREAST FEEDING WORTH SALVAGING?

ALTHOUGH no statistical studies are available to prove the point, there would seem to be little doubt that the incidence of breast feeding in the United States is progressively declining. If so, the reason seems clear enough. It is that artificial feeding has become so simple, safe, and successful that breast feeding no longer seems worth the bother. As of today it would appear that, with the exception of a few centers where there is an interested personnel, breast feeding is largely restricted to what might be termed "natural nursers"—those women who are so physiologically and psychologically constituted for nursing that they attain success whether or not they receive professional advice and assistance. The many others who start out so hopefully abandon the task after a few days or weeks, usually because some minor difficulty is encountered which could have been anticipated and prevented. In the last half century, artificial feeding has received a tremendous amount of attention, while breast feeding has received relatively little. And yet, the techniques necessary for successful lactation in a majority of mothers are known and their effectiveness has repeatedly been demonstrated.

Are we placidly to accept the present trend of gradual replacement of breast feeding by artificial feeding, or should an attempt be made to reverse it? The purpose of this editorial is to obtain an expression of opinion from as many as possible who have any strong feelings in the matter—pro or con. Last October in Miami at the Academy's annual session, the Committee on Medical Education held a round-table discussion on Pediatric Education. The decline of breast feeding was cited as an example of inadequate education. Professors Moncrieff of London and Wallgren of Stockholm were in the audience. Professor Moncrieff stated that approximately 40 per cent of women in England nurse their infants, but that Waller in his hospital had been able to increase this figure to nearly 80 per cent. Professor Wallgren said that some 90 per cent of Scandinavian women breast feed their babies. He indicated that it was largely through the efforts of the public health nurses that such results were achieved. A nationally known pediatrician of wide clinical experience then posed the query, "Why should American women nurse their babies"?—clearly implying in his question that artificial feeding is equally as satisfactory as breast feeding. The incident serves admirably to point up the issue we have in mind—techniques to promote breast feeding are available but is it worth the effort to try to put them into effect on a national scale?

In attempting an answer to this question, several other questions immediately present themselves for consideration. What, for instance, would be involved in an educational

campaign to establish in the obstetrical departments of the country the techniques which have been demonstrated to be successful? What are those techniques and why is breast feeding a failure for so many American women?

Taking up the last question first, we would say from our own experience that the low incidence of breast feeding among American women is not the result of lack of willingness on the part of the women themselves, but is due to other factors. Most primiparas—perhaps four out of five—express a desire to breast feed, only to be defeated in the first few days or weeks under the system of neonatal care which prevails in a majority of our hospitals today. Prominent among these factors is the lack of a hospital personnel really interested in promoting breast feeding. Here the medical profession must share the blame with the nursing profession. We have the impression that few pregnant women discuss with their obstetricians what pre-partum preparations they should make for nursing. We venture the opinion also that few nursing staffs have among their number one or more nurses especially skilled in breast feeding, and available for advice and assistance in the immediate post-partum period when such services are particularly important. Manual expression of the breasts has been advocated since the days of Sedgewick, some thirty years ago, as an effective means of stimulating the flow of milk, and yet we feel safe in estimating that in only a handful of the newborn nurseries of the nation is there a nurse who is skilled in this art and who can teach it to mothers. In the nurseries with which we are familiar, the time of even graduate nurses is largely consumed carrying babies to and fro between the nursery and the mothers' rooms. Presumably this is the general situation, made necessary by the shortage of nurses, but it would seem that such unskilled services could be advantageously relegated to others, making available some of the time of the trained nurse for parent education.

Still another factor, influencing adversely the incidence of breast feeding, is the present custom of discharging mothers from the hospital on the fifth post-partum day. Rarely have the problems of breast feeding been resolved by this time, with the result that their further solution becomes the responsibility of the mother at home. Resumption of household duties plus concern over her infant's welfare is not conducive to milk secretion. Little wonder that breast feeding takes such a nose dive in this period. Waller prefers to keep his mothers in the hospital for ten to fourteen days until lactation has been securely established. With the high incidence of hospital deliveries and with the present costs of hospitalization, it is undoubtedly out of the question to expect to keep American mothers who wish to nurse their babies in the hospital for any such length of time, but at least one of the major causes for the defeat of breast feeding ought to be recognized.

The techniques for securing lactation on a sound basis, and by this is meant mothers who can nurse their babies from four to six months, have been well stated by Waller. We may refer to them briefly here. In his

hospital, preparations for nursing are begun in the latter months of pregnancy. Manual expression is taught, and all primiparas express colostrum from their breasts during the last two months. Special breast shields are worn to correct retracted nipples. Post-partum, every precaution possible is taken to prevent sore nipples. Painful engorgement receives careful attention, with hormonal treatment if necessary. Stasis in the ducts and alveoli is avoided by manual expression of the breasts during the "coming-in" and establishment phases of lactation. Every effort is made to avoid concern and worry on the part of the mother. Assistance and advice are readily available both from the medical and nursing staffs. Let us remember that measures as simple as these have resulted in Waller's hospital in 77 per cent of primiparas nursing their babies for six months. There is nothing complicated or difficult about these requirements. Mainly what is necessary are people who are interested in helping mothers who want to breast feed.

Many, we suppose, will say that the best solution to the problem under discussion is "rooming-in." With this we readily agree, but "rooming-in" in the rank and file of the obstetrical departments of the country is a long way off. In the meantime, we are interested in sounding out opinions about breast feeding vs. artificial feeding. Should we be satisfied with the status quo or should we attempt an educational campaign of national proportions in the hope that the present downward trend of breast feeding might be checked and possibly started in an upward direction? We are aware that articles appear in the medical literature from time to time extolling the advantages of breast feeding, but obviously this approach is not effective. What we have in mind is a program similar to that conducted by the Committee on the Fetus and Newborn of the American Academy of Pediatrics. This group has prepared a manual on standards for nurseries in the care of newborn and premature infants, and this has been widely circulated among the obstetrical departments of hospitals throughout the United States. Perhaps the Academy could be persuaded to set up a Committee on Breast Feeding which would prepare a manual on the techniques of breast feeding and which could be given equally wide distribution. It would be our hope that a manual which spelled out in detail the techniques necessary for successful lactation readily available to house and nursing staff would result in the establishment of more interested personnel in the problems of breast feeding.

The JOURNAL invites your comments.

L. F. H.